Effect of encasings on allergen load, clinical variables and quality of life variables within an atopic population

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Effect van hoezen op de allergeen hoeveelheid, klinische variabelen en kwaliteit van leven variabelen in een atopische populatie.

(met een samenvatting in het nederlands)

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Voor mijn ouders

Content

Chapter 1

General introduction

Introduction

The natural history and occurrence of allergic diseases is characterised by the allergic march.[1;2] There is a typical sequence of sensitisation and manifestation of symptoms that occur in a certain age period and often show a tendency for spontaneous remission with age. In the first decade of life most allergic diseases have started. A meta-analysis study within the atopic population shows that the onset of atopic dermatitis (AD) predominantly occurs in the first year of life in 79.8 % of the patients. Whereas allergic asthma (AA) starts in the first year of life in 41.8 % of the patients and within the eighth year 92.5 % have asthma. In the first year of life 35 % of the atopic patients have allergic rhinitis (AR) and in those aged 2-5 years 59 % have AR.[1]

Not much data were available concerning prevalence of atopic diseases within the population.[3-6] The only random study concerning prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema was described in 1998, the International Study of Asthma and Allergies in Childhood (ISAAC).[3;4] A group of 463 801 school children aged between 13-14 years in 56 countries had to fill in a one-paged questionnaire about symptoms of the three atopic disorders. The prevalence of AA varied from 1.6-36.8 %, AR 1.4-39.7 % and AD 0.3-20.5 %. The highest prevalence of AA was found mainly in English-speaking centres in western countries, the highest prevalence of AD included centres from Scandinavia and Africa, the highest prevalence of AR was reported from centres scattered across the world. The prevalence of allergic comorbidity was not reported in this study.

The European academy of allergology and clinical immunology (EAACI) nomenclature task force has recently proposed a revised nomenclature for allergy. Although the use of the proposed terms is clear, the diagnosis of the allergic diseases might still provide some problems. The task force defines atopy as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, mostly proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis. Allergy is a hypersensitivity reaction initiated by immunologic mechanisms and can be divided in IgE-mediated and non-IgE-mediated allergy (e.g. mediated by IgA, IgM, and IgG or being cell-mediated).[7]

Defining the allergic phenotype

The ongoing investigation of genetic mechanisms of AR, AA and AD requires strict definitions of these phenotypes to allow genetic fingerprinting of the pathogenesis and pathophysiology of these diseases. The expression of the phenotype may be triggered by environmental factors. And the occurrence of several phenotypes within one patient dependent of age, “the allergic march”, makes it even more difficult.[2] Standardised defining criteria for AR are not available at the moment, most important factors in the diagnosis of AR are closely related to nasal and ocular symptoms, rhinorrhea, sneezing, sniffing, impaired sense of smell, blocked nose, itchy nose and postnasal drip.[8;9]

An algorithm has been developed to differentiate the AA phenotype from other lung diseases to classify subjects for genetic epidemiological studies, on the basis of five clinical or laboratory findings: 1 airway hyperresponsiveness (AHR); 2 cigarette smoking; 3 asthma symptoms; 4 airway obstruction; 5 reversibility to a bronchodilator. Five classes were used: 1 definite asthma; 2 probable asthma; 3 unclassified airway disease; 4 COPD; 5 unaffected.[10] According to the taskforce, asthma mediated by immunologic mechanisms (early and late asthmatic reactions) should be called allergic asthma (AA) and if there are indications of IgE-mediated mechanisms the term should be IgE-mediated asthma.[7]

Hanifin and Rajka defined major and minor diagnostic criteria for AD, based on 24 clinical symptoms and signs. Subjects must have three out of four major features and three of the minor features.[11] For clinical purposes a shorter table was developed in the UK (Table 1).[12-15] The taskforce proposed the term atopic eczema/dermatitis syndrome (AEDS) for this disease.

Table 1: The Hanifin and Rajka refined diagnostic criteria for AD[12-15]

Major criterion An itchy dry skin condition in the last 12 months.
In combination with three or more minor criteria: 1 Onset below the age of two* 2 History of flexural involvement 3 History of generally dry skin 4 Personal history of other atopic disease** 5 Visible flexural dermatitis

* Not used in children under four years of age.

** In children aged under four years, history of atopic disease in a first-degree relative may be included.

Clear international criteria for defining AR, AA and AD are not available at the moment. However, different countries and studies use more or less similar criteria for AA.[16] The ideal criteria for defining AR, AA and AD should use disease specific symptoms combined with clinical tests and these tests should be independent of disease activity. Hyper-reactivity tests for AA[16-18] and AR[19;20] are available, but the definition of AD is still dependent of disease activity at the moment patients are seen in the hospital, combined with a patient history as described by Hanifin and Rajka.[11] Hyper-reactivity tests with a high accuracy are not available for AD at the moment.

In the Dutch Mite Avoidance Study (DUMAS) (chapter 2, 3, 7 and 8) the atopic history of the patient is combined with clinical atopic disease activity. So, AR patients must have had AR disease activity in the past 12 months combined with a positive nasal provocation test as described by Lebel[21]. AA patients must have had AA disease activity in the past twelve months combined with a Pc20 methacholine of 9.8 mg/ml or less or adenosine of 80 mg/ml or less or a reversibility of 9%.[22-24] AD patients must fulfil the Hanifin and Rajka criteria

combined with a history of AD symptoms in the past twelve months and a Leicester Sign Score (LSS, a dermatitis score).[25-28] of at least 1 % extent of the body surface and 6 points severity.

Pathogenesis of allergy

Allergens are antigens that initiate and elicit an IgE mediated immunological reaction and are pinocytosed by macrophages and dendritic cells, functioning as antigen presenting cells (APC's), that present the antigens to T-cells. The T cells recognise specific amino acid sequences of the peptides presented in the cleft of Major Histocompatibility (MHC) class II protein of the APC resulting in the differentiation of the naive T cell to a cytokine- and/or interleukin (IL) producing T cell which regulates and determines the nature of the allergic responses. Activation of the naive CD4+ T helper cell (Th0) may result in two distinct Th subsets. These Th subsets are identified according to their interleukin (IL) production, the Th1 cells secrete predominantly IFN-γ and IL-2 (activator of macrophages and T-cells) and Th2 cells secrete IL-4 (promoting IgE switching by B cells) together with IL-5 (causing eosinophil differentiation, activation and prolonging eosinophil survival).[29] It is widely believed that AR, AA and AD are the result of Th2 polarisation of the immune response, although some authors stated that the chronic phase of AD might be the result of chronic inflammation caused by Th1 cells preceded by an acute phase orchestrated by Th2 cells.[30;31]

Environmental allergens

The prevalence of atopic diseases has increased in the last three decades in many countries. At the same time, the population has moved indoors in the developed world. In 1989, 714 children of 13 years old underwent skin tests in New Zealand, which has a temperate climate like the Netherlands and the UK, 320 children were atopic. Of these 320 children 72.5 % were sensitised to rye grass pollen (GP); 67.2 % to HDM; 29.7 % to cat; 14.1 % to alternaria; and 12.5 % to dog; making HDM the most important indoor allergen.[32] Another study in the same period stated that the majority of skin tested atopic 4-year olds with the same battery of allergens were sensitised to HDM (68.4 %).[33]

Houses have become more insulated because of energy saving programs, resulting in warm, humid conditions indoors, not only creating an ideal environment for people who live in it but also for house dust mites (HDM). Circumstances that determine whether mites can live in a particular microhabitat are temperature, humidity and the availability of food (skin scales, oils and other lipids digested by fungi and bacteria). The stages of the HDM life cycle are the egg stage, a six-legged larva stage, two eight-legged nymphal stages and adult male or female stage. At optimum conditions (75-80 % relative humidity and 20-30 degrees Celsius) the egg to adult development of the Dermatophagoides pteronyssinnus takes 3-4 weeks. The adults live about 6 weeks and in that period the females produce each 40-80 eggs.[34;35] In general, beds in homes contain the most mites and allergens.[36] In temperate climates the most common house dust mites are Dermatophagoides pteronyssinnus, Dermatophagoides farinae and Euroglyphus maynei.[34] The antigen of HDM where the majority of sera of individual HDM allergic patients reacts to is called the major allergen, for Dermatophagoides pteronyssinnus

and Dermatophagoides farinae this is Der p1 and Der f1, respectively. Both induce cross-reacting and species-specific antibodies.[37]

Lack of ventilation increases also the airborne concentration of different allergens leading to a higher exposure, sometimes even above personal allergen sensitisation threshold levels. Sensitisation threshold levels vary among the population, in nonatopic children high levels of Der p1 (> 60 μg/g dust) formed a significant risk, in children already sensitised to other allergens threshold levels of > 2 μg/g Der p1 formed a risk.[38;39]

There might be a hierarchy of indoor allergens. The risk of asthma in children sensitised to cats as compared to those sensitised to mites was much lower in the regions with high mite allergen exposure, but similar in regions with relative low Der p1 levels. Apparently, the presence of mite allergens in homes surpasses the effect of other allergens.[40] HDM can also play an important role in inducing and maintaining AD, either by penetration of HDM through a damaged stratum corneum[41-44]or by the crossing the respiratory barrier.[45-47]

The atopy patch test (APT) is a clinical model to demonstrate the induction of AD by epicutaneous application of relevant allergens. This model was for the first time described by Mitchell et al[48] and further developed by Bruijnzeel-Koomen et al.[49] Eczematous lesions can be induced by applying purified allergen of house-dust mite over 48 hours[49], which penetrate the skin and bind to surface bound antigen-specific IgE on Langerhans cells, subsequently antigen specific Th2-cells in the dermis are activated, this is followed by and influx of Th1 cells, macrophages and eosinophils.[44;50;51] On the other hand a worsening of skin symptoms can also be induced after bronchial inhalation of HDM. One open trial study showed an increase of the 'Costa score' 24 hours after allergen challenge[46;47] and a double-blind, randomised placebo controlled study showed exacerbation and newly developing AD lesions 1.5 till 17 hours after challenge.[45]

Colloff gave in 1992 an overview of measures to control mites and their allergens.[35] Hepafilters; ionisers; rigorous ventilation in temperate climates; special dry or wet vacuum cleaners with 1 μm pore filters; could not be recommended, although vacuum-cleaning 2 times a week did result in a 53 % decline in Der p1.[35;52] Other possibly effective methods were washing above 58 degrees Celsius; acaricides and encasings.[35] A more recent meta-analysis of house dust mite control measures in the management of asthma performed in 1998 led the authors to the conclusion that current chemical (acaricides) and physical methods (vacuum cleaning, heating, barrier methods or air filtration systems) aimed at reducing exposure to allergens from house dust mites, seemed to be ineffective in improving asthmatic symptoms. These methods could not be recommended as prophylactic treatment for asthmatic patients who are sensitive to mites. This study combined different physical methods in the analysis therefore no conclusions could be drawn about the use of encasings in particular.[53] Other studies recommended impermeable covers as the most effective treatment in reducing the Der p1 load in bedding[54] and that the use of acaricides might be less effective.[55;56] Table 2 gives an overview of the published randomised HDM encasing studies till the end of DUMAS

(1999). In these studies the HDM outcome variables to demonstrate the effect of avoidance measures were evaluated differently. Treatment effects were tested either compared to baseline levels or between different treatment groups. This resulted in different significant and not significant outcomes (Table 2). In my opinion, in the evaluation of HDM avoidance treatment effects there should be a significant decrease in HDM allergens between placebo and active treatment groups and the study should at least last 12 months to avoid seasonal effects. Only the study of Ehnert et al.[55]fulfils this criterion. The number of patients in the study of Cloosterman et al.[57] combined with the difference in decrease of Der p1 at the end of the study between placebo and treatment groups, suggests that the between groups analysis might also be statistically significant. Ehnert et al.[55] showed an improvement in the Pc20 while Cloosterman et al.[57] did not. Tan[25]was the only study that showed improvement of AD after applying avoidance measures for 6 months. In this thesis the effects of encasings were studied in a randomised double-blinded placebo controlled manner during a period of 12 months on AA and AD.

Table 2: Overview of randomised HDM avoidance studies till end DUMAS (1999) on house dust mite outcome measures.

	Mattress				**Bedroom**				**Living room**			
Author	**Outcome measure**	**Start level**	**End level**	**θ%**	**Outcome measure**	**Start level**	**End level**	**θ%**	**Outcome measure**	**Start level**	**End level**	**θ%**
Ehnert 1992[55]	Der p1 + f1 A	n.p.	n.p.	-98 sign.*	Der p1 + f1 A	n.p.	n.p.	n.d.	Der p1 + f1 A	n.d.	n.d.	n.d.
	Der p1 + f1 AC	n.p.	n.p.	0 n.s.*	Der p1 + f1 AC	n.p.	n.p.	n.d.	Der p1 + f1 AC	n.d.	n.d.	n.d.
	Der p1 + f1 P	n.p.	n.p.	0 n.s.	Der p1 + f1 P	n.p.	n.p.	n.d.	Der p1 + f1 P	n.d.	n.d.	n.d.
Marks, Tovey 1994[58]	Der p1 A (ng/g dust)	15500 (8300-29000)	550 (260-1160)	-96.5 n.s.*	Der p1 A (ng/g dust)	9600 (4600-20000)	1230 (470-2580)	-87 n.s.*	Der p1 A (ng/g dust)	10600 (4500-23200)	1530 (530-4430)	-86 n.s.*
	Der p1 P (ng/g dust)	25700 (13500-49200)	890 (620-1280)	-96.5 n.s.*	Der p1 P (ng/g dust)	11800 (6100-23100)	1590 (910-2930)	-87 n.s.*	Der p1 P (ng/g dust)	6300 (3200-12300)	2340 (760-7150)	-63 n.s.*
Tan 1996[25]	Dust (mg/m^2) weight A	386 (277-690)	9 (4-20)	-98 sign.	Der p1 A (ng/g dust)	3669 (16-42014)	249 (0-15625)	-91 n.s.*	Der p1 A (ng/g dust)	1321 (0-30130)	271 (0-4270)	-76 n.s.*
	Dust (mg/m^2) weight P	361 (243-534)	269 (193-375)	-16 sign.	Der p1 P (ng/g dust)	2161 (32-36756)	225 (0-18063)	-89 n.s.*	Der p1 P (ng/g dust)	931 (54-22391)	271 (7-6726)	-38 n.s.*
Shapiro 1999[59]	Der p1 +f1 A	n.p.	n.p.	-19.6 n.s.	Der p1 +f1 A	n.p.	n.p.	n.d.	Der p1 +f1 A	n.p.	n.p.	n.d.
	Der p1 + f1 P	n.p.	n.p.	+33 n.s.	Der p1 + f1 P	n.p.	n.p.	n.d.	Der p1 + f1 P	n.p.	n.p.	n.d.
Cloosterman 1999[57]	Der p1 A (ng/g dust)	860 (537-1376)	n.p.	-90.6 sign.	Der p1 A	n.p.	n.p.	-33.5 sign.	Der p1 A	n.p.	n.p.	-48.5 sign.
	Der p1 P (ng/g dust)	931 (602-1439)	n.p.	-31.5 sign.	Der p1 P	n.p.	n.p.	0 n.s.	Der p1 P	n.p.	n.p.	0 n.s.
van Lynden van Nes 1999[60]	Guanine A	0.5 (0.1-5.5)	0.2 (0.1-0.3)	-60 sign.	Guanine A	n.p.	n.p.	n.d.	Guanine A	n.p.	n.p.	n.d.
	Guanine P	0.5 (0.1-2.2)	0.3 (0.1-1.8)	-40 n.s.	Guanine P	n.p.	n.p.	n.d.	Guanine P	n.p.	n.p.	n.d.

Abbreviations and annotations

A= Active treatment
AC= Acaracide treatment
n.d.= not done
n.p.= not presented
n.s.= not significant compared to baseline
n.s.*= not significant between groups analysis
P= placebo
sign.= significant compared to baseline
sign.*= significant between groups analysis
θ% = delta percentage change

Table 3: Overview of randomised HDM encasings studies till end DUMAS study (1999).

Author	**Study protocol and study period**	**Patient age**	**Atopic disease**	**Intervention**	**N**	**Clinical effect**
Ehnert[55] 1992	RCT 1 year	7-15 year	AA	1 Encasings 2 acaricides	24	1 Pc20 improved 2 Pc20 no improvement
Marks, Tovey[58] 1994	RPCT 6 months	13-60 year	AA	Encasings, acaricides	35	FEV1 no improvement Pd20 no improvement
Tan[25] 1996	DBPRCT 6 months	7-65 year	AD	Encasings, acaricides	60	LSS severity and extent (bigger decrease in active treatment group) improved
Shapiro[59] 1999	DBRCT 1 year	6-16 year	AA	Encasings, tannic acid	36	FEV1 no improvement Pc20 improved
Cloosterman[57] 1999	RPCT pt and lungfunction technicians blinded 20 weeks	16-60 year	AA	Encasings, acaricides	157	FEV1 no improvement PEF no improvement Pc20 no improvement
Van Lynden-van Nes[60] 1999	RCT 1 year	4-7 year	AA	Encasings, acaricides	27	No improvement

Abbreviations:
AA= Allergic asthma
AD= Atopic dermatitis
AR= Allergic rhinitis
FEV1= Forced expiratory volume in 1 second
LSS= Leicester sign score (an dermatitis score)
PD20= Provocative doses causing a 20% fall in FEV1
PEF= Peak expiratory flow
Pt= Patient
DBPRCT= Double blinded randomised placebo controlled trial
RCT= Randomised controlled trial
RPCT= Randomised placebo controlled trial

Quality of life

Quality of life (QoL) instruments are becoming important in the evaluation of therapy. They can be distinguished in disease-specific and generic instruments. Disease specific instruments are believed to be more sensitive for changes due to intervention within a diagnostic group, while generic are predominantly tailored to general well being.[61]
This thesis focuses mainly on the QoL of AD patients. Chronic skin diseases impair QoL as has been assessed with different QoL questionnaires. The European Academy of Dermatology and Venereology (EADV) has subscribed to the viewpoint that QoL assessment in treatment of skin diseases is important. They proposed the following recommendations: dermatologists should incorporate health-related quality of life measurements to help assess and monitor the progress of their patients; research is required to develop and refine such health-related quality of life instruments and therapy should clearly demonstrate a positive influence on health-related quality of life.[62;63] The British association of dermatologists already tried to properly implement and evaluate these guidelines.[64;65]

As already mentioned different atopic phenotypes can occur within one patient. To measure the combined impact of atopic diseases within one patient it might be recommended to use generic instruments. One of the most widely used generic quality of life instruments is the SF-36 having been developed from the Rand Corporation's Health Insurance Experiment in the USA in 1992. The SF-36 measures health-related quality of life comprises eight dimensions. These eight dimensions are: 1 physical functioning(PF): limitations in physical activities because of health problems; 2 role-physical functioning(RP): dealing with limitations in usual role activities because of physical health problems; 3 bodily pain (BP); 4 general health perceptions (GH); 5 vitality (VT): indicating lack of energy and fatigue; 6 social functioning(SF): with regards to limitations in social activities because of physical or emotional problems; 7 role-emotional functioning(RE): on limitations in usual role activities due to emotional health problems; and 8 mental health (MH).[66-69]

Several questionnaires were developed and used in clinical trials. The German Questionnaire of Coping with Skin Disease (QCSD), a 42-items disease-specific self-administered survey instrument intended for AD only, with 5 scales: social stigmatisation, restrained emotional coping with the disease, general emotional distress, awareness of restriction in active, problem-related coping, impact on QoL.[70] A variant of this questionnaire with 51 items was used in other studies.[71;72] The most well-known questionnaire has been the Dermatology Life Quality Index (DLQI) having developed by Finlay and Kahn 1994 which was intended as a compact organ specific self-administered questionnaire suitable for patients with any skin disease (acne, psoriasis, AD).[43] It comprises six dimensions of ten items altogether dealing with: 1 symptoms and feelings, 2 daily activities, 3 leisure, 4 work and school, 5 personal relationships and 6 treatment. Also a children's variant, i.e. the CDLQI was developed, [73;74]

Aim and outline of the thesis

The aim of this thesis was to elucidate the effect of encasings on allergen load, clinical and quality of life variables within an atopic population.

Two study populations are described in this thesis:

a) Patients with allergic asthma recruited in the Asthmacenter Heideheuvel.
b) Patients with allergic asthma, allergic rhinitis and/or atopic dermatitis recruited in a multi-center study on allergen avoidance (Dutch Mite Avoidance Study: DUMAS, performed in Utrecht, Rotterdam and Groningen).

In this respect the following research questions were addressed:

1 What is the number of the atopic phenotypes of the study population and can questionnaires, addressing atopic symptoms, predict the prevalence and comorbidity of the atopic diseases? Chapter 2 describes the results of the total study population of the DUMAS study.
2 Does active treatment, consisting of applying encasings around pillows, duvets and mattresses, have an effect on clinical and immunological outcome measures in an AD population? Chapter 3 describes the results of the AD populatio of the DUMAS study.
3 Does active treatment, consisting of applying encasings around pillows, duvets and mattresses, have an effect on clinical asthma and rhinitis variables, immunological and QoL variables in an AA and AR population? Chapter 4, 5 describe the results of the Asthmacenter Heideheuvel study.
4 Which questions of the QCSD relate to particular factors and are generic and disease specific questionnaires both necessary to measure QoL?.
5 What is the effect of extent and severity of AD, exposure to HDM, age, encasings and gender on QoL as measured with the generic SF-36 or disease specific QCSD questionnaire? Chapter 6, 7, 8 describe the results of the AD population of the DUMAS study.

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Chapter 2

Presence of clinical symptoms within an atopic population sensitised to house dust mite who reported symptoms of allergic asthma, allergic rhinitis and atopic dermatitis, using a questionnaire.

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Submitted

Presence of clinical symptoms within an atopic population sensitised to house dust mite who reported symptoms of allergic asthma, allergic rhinitis and atopic dermatitis, using a questionnaire.

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Abstract

Background: Several studies used questionnaires to estimate the prevalence of phenotypes of atopic diseases. There is a lack of data concerning the relation between reported and clinical symptoms.

Objective: To study the presence of clinical symptoms within an atopic population sensitised to house dust mite (HDM) who reported specific allergic symptoms of allergic asthma (AA), allergic rhinitis (AR) and atopic dermatitis (AD).

Methods: HDM sensitised patients (8-50 years) filled in a questionnaire with specific core questions concerning symptoms of AR, AA and AD. Each patient underwent a nasal provocation test with HDM, a bronchial provocation test with methacholine and adenosine, together with a specific dermatitis score (the Leicester Sign Score, LSS). Also the reversibility after 400 μg (children) or 800 μg salbutamol inhalation was measured.

Results: In this study 325 HDM sensitised patients are included. The prevalences of the clinical atopic diagnoses in decreasing are 33.5 % AR; 31.4 % AR and AA; 12.0 % AR combined with AA and AD; 8.9 % AR and AD; 5.8 % AA; 3.7 % AD; 2.2 % AA and AD, 2.5 % has no clinical atopic disease activity according to the stated criteria. Eighty-four patients have a different reported diagnosis (using questionnaires) compared to the clinical diagnosis (using questionnaires combined with provocation and scoring tests). In the majority comorbidity is present, 72.3 % (235 patients) in the reported diagnoses groups and 54.5 % (177 patients) in the clinical diagnoses groups.

Conclusions: The AR phenotype has the highest prevalence within this HDM sensitised population and AA combined with AD the lowest. In the majority of the study population comorbidity is present. The majority of the patients have positive tests corresponding to the atopic symptoms they reported in the questionnaires. Using questionnaires as an indication of specific allergic diseases within the population can result in a relatively good estimation of atopic disease activity.

Keywords: Atopic dermatitis, asthma, allergic rhinitis, house dust mite, nasal provocation test, bronchial provocation test, Leicester sign score, comorbidity, airway hyperresponsiveness

Abbreviations

AA Allergic Asthma
AD Atopic dermatitis
AHR Airway hyperresponsiveness
AR Allergic Rhinitis
HDM House dust mite
LSS Leicester sign score (a dermatitis score)

Introduction

Until recently not much data were available concerning prevalence of atopic diseases within the population.[1-4] The only random study concerning prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema was described in 1998 and the study was called the international study of asthma and allergies in childhood (ISAAC).[1;2] A group of 463 801 school children aged between 13-14 years in 56 countries had to fill in a one-paged questionnaire about symptoms of these three atopic disorders. A video asthma questionnaire was also performed within a smaller group.

Important core questions for asthma were: "Have you had wheezing or whistling in the chest in the last 12 months?; for allergic rhinoconjunctivitis: "In the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu? If yes, in the past 12 months, has this nose problem been accompanied by itchy watery eyes?"; for AD: "Have you ever had an itchy rash which was coming and going for at least 6 months? If yes: Have you had this itchy rash at any time in the last 12 months? If yes: Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttock, or around the neck, ears, or eyes?".

The prevalence in the general population of AA varied from 1.6-36.8 %, AR 1.4-39.7 % and AD 0.3-20.5 %. The highest prevalence of AA was found mainly in English-speaking centres in western countries, the highest prevalence of AD included centres from Scandinavia and Africa, the highest prevalence of AR was reported from centres scattered across the world. The prevalence of comorbidity was not reported in this study. Although, not much data are available concerning comorbidity of allergic diseases, some studies reported comorbidity within a pre-selected AA or AD population.[5;6] A Chinese study reported comorbidity of different atopic phenotypes in 392 children who visited a Taiwanese paediatric allergy clinic, the majority (55.6 %) had combined atopic phenotypes.[7] Most studies used questionnaires filled in by patients or their parents in which presence of other allergic symptoms were reported. A disadvantage of usage of questionnaires and self-reported allergic symptoms is that presence of clinical symptoms cannot be easily verified. Selection of patients from organ-specific (ENT, pulmonology, dermatology) outpatient clinics within a certain time-period created another bias.

In the present study we compared diagnoses based on pre-defined criteria using core questions concerning atopic diseases with clinical diagnoses based on questionnaires and provocation tests and scoring systems together.

Materials and methods

Subjects

Patients aged between 8 and 50 years were recruited from the dermatology, allergology and pulmonary outpatient clinic at the University Hospital in Utrecht, Rotterdam and Groningen (the Netherlands), the SAL (a physician laboratory foundation in Utrecht and Groningen), and from the Dutch population which contacted the departments after reading an article about the project in the media in the period 1997-1998. Patients who were included had at least a specific IgE level ≥ 0.7 kU/l for Der p1 or a class I positive pricktest for Der p1.[8] All patients reported symptoms of atopic rhinitis and/or allergic asthma and/or atopic dermatitis.

Reported diagnosis

Two different diagnosis were used, the "reported diagnosis" and the "clinical diagnosis". For the reported diagnosis the self-reported symptoms of AR, AA and AD were used. Core questions for AR were: "Do you have AR with symptoms of sneezing, a runny or blocked nose, itching in the nose when you did not have a cold or the flu? If yes, did you have these symptoms in the last 12 months?"; for asthma: "Do you have asthma and symptoms of wheezing, whistling in the chest or are you on any medication used for asthma? If yes, did you have symptoms of wheezing and whistling in the chest in the past 12 months?" for AD: "Do you have eczema? If yes, do you have any recurrent symptoms of a dry skin and itchy rash localised at the folds of the elbows or behind the knees or other places of the body not caused by allergic contact dermatitis and not caused by hand or foot eczema? If yes, did you have these symptoms in the past 12 months?". Patients could answer these questions with yes, no and in the past.

Clinical diagnosis

For the clinical diagnosis the following criteria were added. AR patients also had to have a positive nasal provocation test as described by Lebel[9]. AA patients also had to have a Pc20 methacholine of 9.8 mg/ml or less or adenosine of 80 mg/ml or less or a reversibility of 9% or more after inhalation of salbutamol[10-12] and AD patients had to have a LSS score[13-16] of at least 1 % extent of the body surface and 6 points severity.

Clinical assessment

Medication

Antihistamines were stopped two weeks before testing or replaced by acrivastine two weeks till 3 days before testing. Patients had to stop short-working bronchodilators 24 hours and long-working bronchodilators 48 hours before testing.

Nasal provocation test

Patients had to wait half an hour prior to the test so that the nasal mucosa could acclimatise. Phosphate buffered solution (PBS) (containing 0.03 % human serum albumin and 0.05 % benzalkonium chloride) was sprayed in each nostril by a nasal pumpspray delivering a fixed

dose of 0.125 ml solution. After 15 minutes house dust mite extracts of 100 Bu/ml, 1000 Bu/ml and 10.000 Bu/ml (ALK-Abello, Spain) were applied and assessed as previously described.[9] We considered the test to be positive when the symptom score after nasal inhalation of 100, 1000 or 10000 BU/ml HDM increased at least three points compared to the symptom score after nasal inhalation of PBS.

Bronchial provocation test

Airway hyperresponsiveness (AHR) was assessed as described earlier by letting patients inhale fixed doses of methacholine (whole population) or adenosine (adult population) during 2 minutes.[12] A concentration causing a fall of more than 20 % in forced expiratory volume in one second (FEV1) was considered as a threshold value.

Reversibility

The forced expiratory volume in one-second (FEV1) was measured before inhaling salbutamol. Children till 18 years old inhaled 400 g and adults inhaled 800 g. After 15 minutes the FEV1 was again measured. An increase of more than 9 % was considered a symptom of asthma.

Leicester Sign Score

We used the Leicester sign score (LSS) for AD divided in a severity score and extent score.[13-16] The following variables were assessed:

Disease activity: Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification) were graded at six defined body sites on a scale of 0 (none) to 3 (severe). These gives a total body disease activity score, the LSS severity score (maximum 108).

Extent of disease: Assessment was made according to the "rule of nines" and resulted in the LSS extent score (maximum 100 %).

Skin tests

The skin prick test (SPT) was used for selecting HDM sensitised patients and performed at the flexor part of the lower arm with standardised HDM extract (10.000 BU/ml)(ALK-ABELLO, Spain). The early response was scored as the wheal diameter 15 minutes after challenge. The reaction on histamine phosphate solution and phosphate buffer diluent served as positive and negative controls. Also specific anti Der p1 IgE was measured in blood.

Results

In table I the general characteristics of the atopic population are presented. Figure I shows the specific anti-Der p1 IgE in the different clinical diagnoses groups. Groups of more than 25 patients are presented in increasing specific anti-Der p1 IgE order. The highest specific IgE was seen in the patient group with all three atopic diseases.

Table I: General characteristics of the study population according to their clinical diagnosis (if not otherwise stated median and range are given).

Atopic disease	**Frequency (N)**	**Age ($\bar{x}$, s)**	**Pc20 methacholine (mg/ml) (median, range)**	**Pc20 adenosine (mg/ml) (median, range) (N)**	**Reversibility % (median, range)**	**LSS severity (max. 108) (median, range)**	**LSS extent (%) (median, range)**	**Nasal score 10,000 BU/ml HDM (max. 12)**
AR	109	29 ± 11	14.5 (0.1-157)	640 (0-640) (61)	2.8 (-4.0-12.2)	0 (0-13)	0 (0-78)	6 (3-10)
AA	19	27 ± 13	1.1 (0.1-7.2)	57.7 (0.9-640) (14)	7.1 (-4.0-28.0)	0 (0-4)	0 (0-27)	2 (-1-10)
AD	12	26 ± 11	28.5 (0.1-157)	640 (26.6-640) (8)	3.9 (-3.0-13.3)	21 (7-60)	33.5 (3-88)	2 (-1-9)
AR + AA	102	25 ± 13	0.9 (0-157)	21.3 (0-640) (50)	6.9 (-9.8-29.5)	0 (0-21)	0 (0-88)	6 (0-12)
AR + AD	29	25 ± 11	4.9 (0.4-157)	640 (6.4-640) (16)	4.4 (-6.7-33.3)	16 (8-33)	18 (3-87)	6 (3-9)
AA + AD	7	24 ± 11	0.8 (0.1-13.3)	35.4 (0.9-640) (5)	9.9 (-0.9-19.1)	35 (8-54)	30 (3-48)	2 (2-9)
AR+ AA + AD	39	26 ± 10	0.4 (0-11.6)	15.5 (0.1-640) (23)	8.9 (-30.3-38.0)	16 (6-70)	21 (2-86)	6 (0-10)
No atopic disease*	8	33 ± 8	103 (4.7-157)	640 (9.0-640) (7)	3.9 (-3.1-6.5)	0 (0-4)	0 (0-9)	2 (0-2)

*No clinical atopic disease

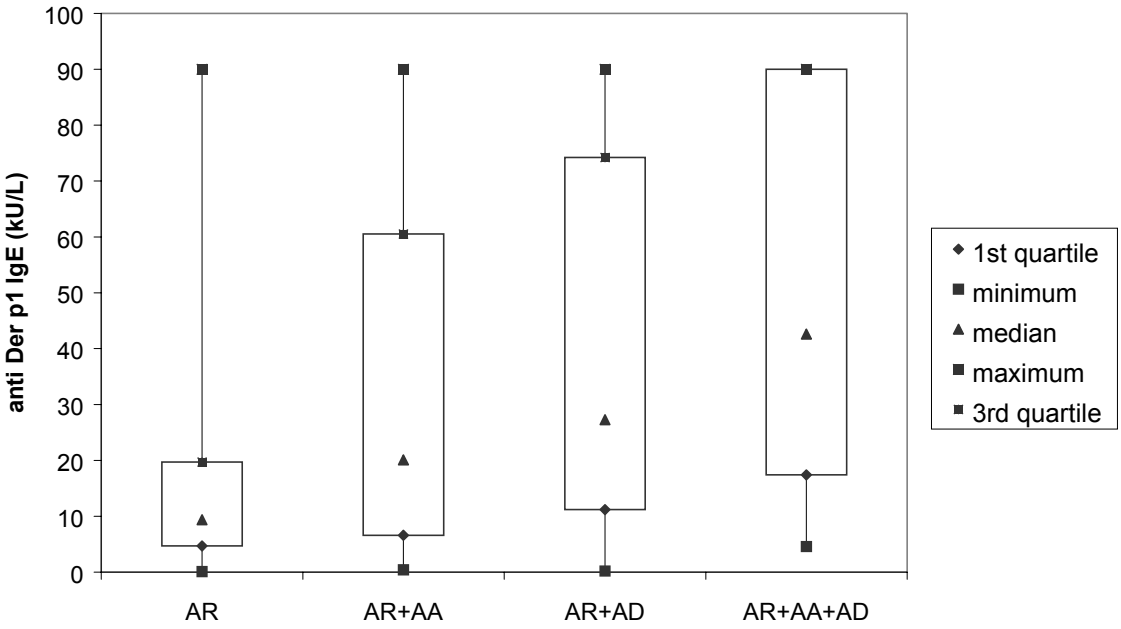

Figure I: Anti-Der p1 IgE (kU/L) in atopic diagnoses groups with more than 25 patients.

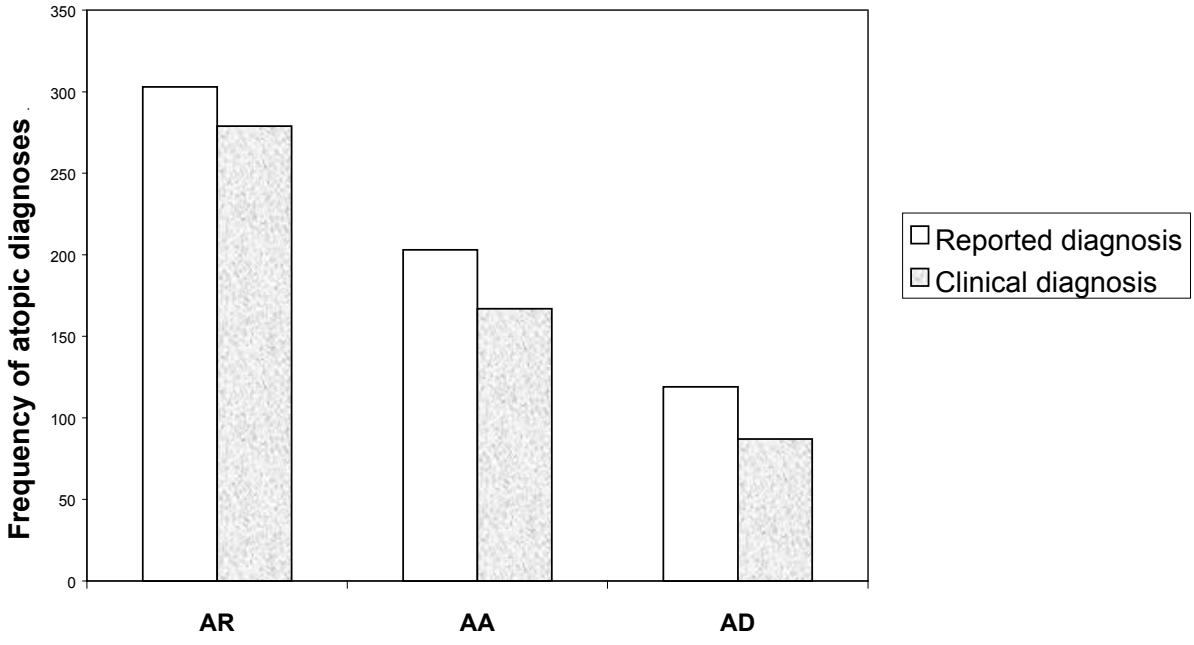

Figure II: Frequency of reported and clinical diagnoses within an atopic population of 325 patients.

Figure II shows the frequency of organ specific reported and clinical diagnoses, because patients reported more than one atopy diagnosis and tested positive for more than one clinical atopy diagnosis, the sum was more than the total number of 325 patients. The frequency of organ specific reported diagnoses were 303 AR, 203 AA, 119 AD; the frequency of clinical diagnoses were 279 AR, 167, AA and 87 AD. For the clinical diagnosis patients had to report atopic symptoms combined with positive tests, which resulted in a loss of organ specific clinical atopy diagnoses compared to reported diagnoses, which can be clearly seen in figure II.

The number of HDM sensitised patients with reported and clinical atopic diagnoses is shown in Table II. The prevalences of the clinical atopic diagnoses in decreasing order are 33.5 % AR; 31.4 % AR and AA; 12.0 % AR combined with AA and AD; 8.9 % AR and AD; 5.8 % AA; 3.7 % AD; 2.2 % AA and AD, 2.5 % did not have clinical atopic diseases. In the majority comorbidity is present, 72.3 % (235 of 325 patients) in the reported diagnoses groups and 54.5 % (177 of 325 patients) in the clinical diagnoses groups. As Table III shows, there was a discrepancy of 25.8 % (84 of 325 patients) between reported and clinical diagnoses.

Table II: Frequency and percentages of reported and clinical atopic diseases.

Diagnosis	**Reported diagnosis**		**Clinical diagnosis**	
	N	%	N	%
AR	78	24.0	109	33.5
AA	5	1.5	19	5.8
AD	7	2.2	12	3.7
AR + AA	124	38.2	102	31.4
AR + AD	37	11.4	29	8.9
AA + AD	10	3.1	7	2.2
AR+ AA + AD	64	19.7	39	12.0
No clinical atopic disease	0	0	8	2.5
Total	325	100	325	100

Table III presents the 84 patients who changed from reported diagnoses groups to other clinical diagnoses groups. The majority (32 patients) who changed from diagnosis group, reported having AD but did not have active AD. Thirteen patients of the group which reported having AR in combination with AA and AD changed to the group with the clinical diagnosis AR and AA; three patients to AR and AD; three patients to AA and AD; four patients to AR, one patient to AA and one to AD. Twenty-four patients of the group with the reported diagnosis AR combined with AA changed to the clinical diagnosis group AR, nine to AA and two did not have clinical atopic disease. Ten patients of the group, which reported having AR combined with AD, changed to the clinical diagnosis group AR and two to AD. Four patients with the reported diagnosis AA combined with AD changed to the clinical diagnosis group AA and two to AD. Six patients with the reported diagnosis AR did not have clinical atopic

disease. Of the 325 patients tested, 84 patients (table III) did have a negative provocation and/or scoring test concerning the symptoms they reported.

Table III: Frequency of patients changing from a reported diagnosis group to clinical diagnosis group.

Reported diagnosis	Clinical diagnosis	N
AR + AA + AD	AR + AA	13
AR + AA + AD	AR + AD	3
AR + AA + AD	AA +AD	3
AR + AA + AD	AR	4
AR + AA + AD	AA	1
AR + AA + AD	AD	1
AR + AA	AR	24
AR + AA	AA	9
AR + AA	No clinical atopic disease	2
AR + AD	AR	10
AR + AD	AD	2
AA + AD	AA	4
AA + AD	AD	2
AR	No clinical atopic disease	6
Total	Total	84

In contrast, 93 patients had a positive provocation and/or scoring test in contrast to the atopic symptoms they reported (adding table IV with table V and table VI results in the 93 patients). Recalculation of the data leads to an even more negative conclusion that only 45.5 % (325 minus 84 patients minus 93 patients results in 148 of 325 patients) did have symptoms belonging to the atopic diagnoses groups they reported at the moment they were tested.

Table IV shows the group with AHR, 71 patients did have AHR without reporting asthmatic symptoms. The largest group consisted of 49 who fulfilled the criteria of clinical AR, 4 of clinical AD and 18 of clinical AR combined with AD.

Table IV: Number of patients with AHR in different clinical atopy diagnoses groups who did not report asthmatic symptoms (median and range).

Clinical diagnosis	N	Pc20 methacholine (mg/ml)	Pc20 adenosine (mg/ml)	Reversibility %
AR	49	2.8 (0.1-157)	36.3 (0-640)	4.0 (-3.1-12.2)
AD	4	2.9 (0.1-28.0)	333 (26.6-640)	5.4 (-3.0-13.3)
AR + AD	18	1.2 (0.4-7.0)	31.2 (6.4-640)	5.9 (-6.7-33.3)

Table V shows another group that had a positive nasal challenge test without reporting AR symptoms. Analysis of this group showed that the four patients with AD had a moderate to high LSS score, median (range) score severity: 20.5 (13-35); extent: 23.5 (18-30). And the nine patients with AA had a low Pc20 methacholine (median, range) 0.6 (0.1-7.2) mg/ml. The high LSS score and low Pc20 methacholine was also present in the group of four patients with AA combined with AD, LSS severity: 46.5 (8-54); LSS extent: 35.5 (3-48); Pc20 methacholine: 1.7 (0.2-13.3) mg/ml.

Table V: Number of patients with a positive nasal challenge test who did not report rhinitis symptoms (max. nasal score is 12)

Clinical diagnosis	N	Nasal score 100 Bu/ml HDM	Nasal score 1000 Bu/ml HDM	Nasal score 10,000 Bu/ml HDM
AA	9	3 (1-7)	4 (3-8)	6 (4-10)
AD	4	1 (-1-6)	3.5 (1-7)	5 (4-9)
AA + AD	4	3.5 (1-5)	5 (3-9)	7.5 (6-9)

A small group of five patients fulfilled the criteria of active AD as measured with the LSS at the clinical testing and scoring moment but did not fulfil the criteria of having had AD in the past 12 months when they had to fill in the questionnaire at intake. Because filling in the questionnaires and the clinical testing took place at two different moments, some patients could have had no AD in the past 12 months but could have a positive AD score at the moment of clinical testing and scoring. Looking at the patient history, all patients reported having had eczema in the past and or had eczema more than 12 months ago according to the reported diagnoses criteria.(Table VI)

Table VI: Number of patients with a positive Leicester Sign Score who did not fulfil the criteria of AD

Clinical diagnosis	N	LSS Severity	LSS Extent
AR	3	9 (8-11)	18 (15-54)
AA + AR	2	16.5 (12-21)	45.5 (3-88)

A small group of five patients fulfilled the criteria of active AD as measured with the LSS at the clinical testing and scoring moment but did not fulfil the criteria of having had AD in the past 12 months when they had to fill in the questionnaire at intake. Because filling in the questionnaires and the clinical testing took place at two different moments, some patients could have had no AD in the past 12 months but could have a positive AD score at the moment of clinical testing and scoring. Looking at the patient history, all patients reported having had eczema in the past and or had eczema more than 12 months ago according to the reported diagnoses criteria.(Table VI)

Discussion

The frequency of organ specific reported diagnoses (using questionnaires) were 303 AR, 203 AA, 119 AD; the frequency of clinical diagnoses (using questionnaires combined with clinical tests and scores) were 279 AR, 167, AA and 87 AD. For the clinical diagnosis patients had to report atopic symptoms combined with positive tests, which resulted in a loss of organ specific clinical atopy diagnoses compared to reported diagnoses. As expected there was a discrepancy of 25.8 % (84 of 325 patients) between reported and clinical. Adding the 93 patients, with a positive clinical score who did not report (using the questionnaire) particular atopic symptoms belonging the atopic symptoms of clinical tests, to the 84 patients, who did have negative clinical tests but reported the presence of particular atopic symptoms, resulted in a discrepancy between reported and clinical diagnoses of 45.5%. However, in clinical practice patients are diagnosed of having AR, AA or AD when they report symptoms of these diseases during a longer period, as such we should use the discrepancy of 25.8 %. Clinical tests in itself still do not determine the diagnosis of the patient and the clinical diagnosis should be a combination of reported symptoms and tests.

In this study the prevalences of the clinical atopic diagnoses in decreasing order are 33.5 % AR; 31.4 % AR and AA; 12.0 % AR combined with AA and AD; 8.9 % AR and AD; 5.8 % AA; 3.7 % AD; 2.2 % AA and AD. In the majority comorbidity is present, 72.3 % (235 patients) in the reported diagnoses groups and 54.5 % (177 of 325 patients) in the clinical diagnoses groups. The high atopic comorbidity suggests that we should speak of an atopic syndrome and that patients need a multidisciplinary approach.

The criteria of clinical AD were very strict, patients had to have active AD at the time they visited the clinic for testing. At the moment they were tested the majority of patients (n=32) who changed from diagnosis group, reported having AD but did not have active AD using the LSS (6 points severity and 1 % extent), making it necessary to develop tests that can detect “primed” skin. In contrast to AA, AR there is no functional test sensitive enough to measure hyperreactivity of the skin in AD. So the only objective criterion is the presence of symptoms. However, according to the Hanifin and Rajka[8] criteria patients can have AD without having any symptoms at a particular moment. Different tests like transepidermal water loss; skin blood flow measurements; infrared spectroscopy and impedance spectroscopy; have already been proposed but they are difficult to interpret and not yet used for clinical practice.[17-19]

Testing and scoring of atopic disease activity at a particular moment gives a random indication of disease activity, which may lead to underestimation of the prevalence of an atopic disease. However, this study might give an indication of disease activity within the atopic group as a whole. In other words, 241 of 325 patients (74.2 %) reported symptoms of a particular atopic disease in the questionnaire and had clinical symptoms corresponding to the atopic disease they reported at the moment they were tested. Because atopic patients were included during the whole year, seasonal effects on presence or absence of atopic symptoms could probably be excluded.

A considerable number of patients who did not experience asthmatic symptoms showed AHR. The largest group without AA but with AHR fulfilled the criteria of clinical AR. The two other groups with AHR had AD or AR and AD, AD might have a large impact on quality of life that could have led to under-reported AA. These diagnoses groups might represent a population with mild asthmatic symptoms not severe enough to cause any symptoms leading to a doctor's consultation. Several studies showed that patients with AR have increased airway responsiveness.[20-22] Some even suggesting that individuals with AHR may be in a latent phase of asthma that may become clinically active over the course of time.[23-27]

Seventeen patients had a positive nasal provocation test without reporting AR symptoms. The high LSS scores and low Pc20 methacholine suggests that they might not experience AR symptoms severe enough to report.

Five patients reported symptoms of clinical AD without fulfilling the criteria of AD. Looking at the patient history, all patients reported childhood eczema or having had eczema more than 12 months ago according to the criteria stated. Due to the used method, patients had to have a history of a specific atopic disease and had to have had disease activity in the past twelve months (reported symptoms), this could be a group where atopic disease activity might have been underestimated.

In figure I the specific anti Der p1 IgE in the different clinical diagnoses groups is shown. Groups of more than 25 patients are presented in increasing specific IgE order. The results corresponded with earlier published data[7] and indicated that patients with AD are more sensitised to HDM than the group with AR alone or AR combined with AA, suggesting AD is a more severe form of atopic disease than AA or AR.

Conclusions

Questionnaires can lead to an overestimation of atopic disease prevalence probably due to inaccurate memory of the presence of particular atopic symptoms and the period the clinical symptoms occur. However atopic diseases have varying expression, which in contrast can lead to an underestimation of atopic disease prevalence when scoring and testing take place at a particular moment. As such, it is important to compare the reported and clinical diagnoses. Eighty-four patients have a different reported diagnosis compared to the clinical diagnosis, on the other hand 241 of 325 patients have positive provocation and scoring tests in correspondence to the atopic symptoms they reported. Using questionnaires as an indication of specific allergic diseases within the population can result in a relatively good estimation of atopic disease activity.

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Chapter 3

Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind placebo controlled study. Dutch Mite Avoidance Study (DUMAS)

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Summary
Background: House dust mite (HDM) allergen may induce and maintain atopic dermatitis (AD). Reduction of allergen load by applying encasings may improve the clinical symptoms of AD.
Objective: To investigate in a randomised double-blind placebo-controlled study if reducing HDM allergen by mattress, duvet and pillow encasings during 12 months will result in an improvement of AD.
Methods: Atopic dermatitis patients, 8-50 years old and allergic to HDM, having a Leicester Sign Score (LSS, a dermatitis score) of at least 1 % extent and a severity score of 6 points or more, were randomly allocated to an active (n=45) or a placebo allergen-avoidance group (n=41). Avoidance measures consisted of applying HDM-impermeable encasings for mattresses, pillows, duvets and cotton encasings for the placebo group. Effect on the allergen concentrations (Der p1 and Der p1 + Der f1), LSS extent and severity and visual analogue score (VAS) itch, VAS sleeplessness, intradermal test (IDT), atopy patch test (APT), total serum IgE, anti-Der p1 specific IgE and total blood eosinophils were studied.
Results: The active encasings reduced the Der p1 allergen concentration in the mattress after twelve months with a factor 2,1 (p=0,007) and the Der p1 + Der f1 with a factor 2,5 (p=0,005), no significant change in allergen concentrations in the mattress was seen in the placebo group. Although the decrease in allergen load was significant, no differences in treatment induced changes were seen between the placebo and the active group.
Conclusions: Use of HDM impermeable encasings resulted in a significant decrease in Der p1 and Der p1 + Der f1 allergen concentrations. However this reduction in allergen load did not result in significant changes in clinical parameters between the groups. Reduction of allergens in other environments (working, school, outdoors) might be equally important to improve AD.

Keywords: Atopic dermatitis, mattress encasing, randomised double-blind placebo controlled study, house dust mite, allergen avoidance, Leicester sign score

Abbreviations

AA	Allergic Asthma
AD	Atopic Dermatitis
APT	Atopy Patch Test
AR	Allergic Rhinitis
DUMAS	Dutch Mite Avoidance Study
HDM	House Dust Mite
IDT	Intradermal test
MWU test	Mann Whitney U test
VAS	Visual Analogue Scale
WMP test	Wilcoxon matched-pairs signed rank test

Introduction

AD is a chronically relapsing dermatitis with typical morphology and distribution. Hanifin and Rajka defined major and minor diagnostic criteria for AD in 1980 which were generally accpepted.[1] HDM can play an important role in inducing and maintaining atopic dermatitis (AD), either by penetration of HDM through a damaged stratum corneum[2-5]or by the crossing the respiratory barrier.[6-8] The atopy patch test (APT) is a clinical model to demonstrate induction of AD by epicutaneous contact with allergens. This model was for the first time described by Mitchell et al.[9] and further developed by Bruijnzeel-Koomen et al[10]. Eczematous lesions can be induced by applying purified allergen of house-dust mite over 48 h.[10], which penetrate the skin and bind to surface bound antigen-specific IgE on Langerhans cells.[11;12] These cells presented the allergens to T-cells, resulting in a sequential activation of initial T helper 2 (Th2)- and a late phase Th0/Th1-type cells resembling lesional skin.[13;14] The route in which it is activated by allergens must be further elucidated, but studies with atopy patch tests show that the skin can directly be challenged with HDM resulting in AD-like reactions as erythema, papules and vesicles.[2-5]At the other hand a worsening of skin symptoms can also be induced after bronchial inhalation of HDM. One open trial study showed an increase of the 'Costa score' 24 hours after allergen challenge[7;8] and a double-blind, randomised placebo controlled study showed exacerbation and newly developing AD lesions 1.5 till 17 hours after challenge.[6]

Several studies showed a beneficial effect of house dust mite (HDM) avoidance measures on the improvement of atopic diseases. Most studies focussed on allergic asthma and less on allergic rhinitis and AD.[15] Roberts[16] and August[17] reported improvement of clinical symptoms in patients with AD after combinations of the use of plastic encasings, removal of carpets and vacuum cleaning. Tan[18] et al. performed a double-blind controlled trial for duration of 6 months with 60 AD patient in 1993-1994. Both placebo and active treatment reduced significantly the Der P1 concentration after 1 month that lasted 6 months. Although both study groups showed significant reductions in the severity and area affected by AD, the change in the in AD severity score was significantly higher in the active group than in the placebo group.

In this study we tested the hypothesis that mattress, duvet and pillow encasings applied during one year decreased the Der p1 load resulting in a long lasting improvement of AD as measured with the Leicester sign score (LSS).

Patients and methods

Subjects

Patients with AD aged between 8 and 50 years were recruited from the dermatology, allergology and pulmonary outpatient clinic at the University Hospital in Utrecht, Rotterdam and Groningen (the Netherlands), the SAL (a physician laboratory foundation in Utrecht and Groningen), and from the Dutch population which contacted the departments after reading an article about the avoidance project in the media.

Patients who were included had at least a specific IgE level ≥ 0.7 kU/l for Der p1 or a positive skin pricktest (index ≥ 0.7, index is calculated by dividing mean diameter wheal on HDM by the mean diameter wheal on histamine) for Der p1 and AD according to the criteria of Hanifin and Rajka.[1] The specific inclusion and exclusion criteria are stated in table I.
Antihistamine drugs and class 2 topical steroids were allowed between the test periods.

Table I: In- and exclusion criteria

Inclusion criteria	**Exclusion criteria**
1 Atopic dermatitis	1 Pets at home and positive skin test (index ≥ 0.7) and/or RAST ≥ 0.7 for the pet
2 HDM RAST ≥ 0.7 and/or skin test index ≥ 0.7	2 pregnant or lactating
3 Der p1 or f1 ≥ 200 ng/g dust in the dust sample of the mattress	3 daily use of oral steroids
4 no encasings or willing to remove them for the period of the study	4 daily use of cyclosporine

Study design
The study was a randomised double-blind, placebo-controlled trial of 12 months duration, the active treatment consisted of Goratex bedding system (HAL, Haarlem, the Netherlands). The placebo group was given cotton encasings (HAL, Haarlem, the Netherlands). The encasings were applied to the mattress, duvet and pillows on all beds in the patient's room.
The placebo encasings used in this study had an unloaded pore width of 0.1*0.08 millimeter. Applying a force of 200 Newton changed the pore width to 0.1*0.1 millimeter. The allergen barrier of the placebo encasing was 15 % against 98 % of the active encasings. Patients contacted our clinics at three moments. At starting point (T0), after four months (T4) and after twelve months (T12).

Dust sampling
Dust samples were collected over 5 minutes from a 1 square meter area with a vacuum cleaner (Rowenta RS 005 Dymbo, 1200 Watt) containing a 20 μm filter paper in a filter chamber by a blinded study nurse (ALK, the Netherlands). Dust was sampled before treatment, at 4 months and at 12 months from the mattress and floor of the patient's bedroom and from the living room. Dust samples were weighed and stored at –18 ° C until extracted. Der p 1 was measured by a competitive radioimmunoassay as described for grass pollen allergen.[19] For this assay, 50 μl (of a dilution of) the dust extract was incubated at room temperature with 50 μl
of a 1/2500 dilution of a rabbit anti-D.pteronyssinus antiserum. After 2 hrs 1 ng 125I-labelled affinity-purified Der p 1 and 0.5 mg Seharose-coupled Protein A was added. The final reaction volume was 400 μl. After overnight incubation on a mixer, Sepharose-bound radioactivity was measured. The results were compared with an in-house reference calibrated against the WHO reference, assuming that one international unit equals 0.125 ng. The lower limit of detection of this assay is 0.5 ng/ml.

Outcome measures
The primary outcome was the clinical skin score. The secondary outcomes were the early allergic responses to the intradermal test with Der P1, the atopy patch test with Der P1 and the visual analogue scores on itch and sleeplessness, total serum IgE, specific serum IgE against Der p1 and total blood eosinophils.

Clinical assessment
Patients were evaluated at the start of the study and four and twelve months there after. We used the Leicester sign score (LSS) for AD divided in a severity score and extent score. [18;20]
The following variables were assessed:
Disease activity: Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification) were graded at six defined body sites on a scale of 0 (none) to 3 (severe). This gives a total body disease activity score, the LSS severity score (maximum 108).
Extent of disease: Assessment was made according to the "rule of nines" and resulted in the LSS extent score (maximum 100 %)
Sleep and itch: At each visit the patients rated their symptoms of itch and loss of sleep during the preceding two weeks on a visual analogue scale (0-100 mm).[21-23]

Skin tests
The intradermal test (IDT) and skin prick test (SPT) were performed at the flexor part of the lower arms with standardised HDM extract (30 BU/ml (2.94 10^{-2} μg/ml), 0.03 ml and 10.000 Bu/ml (9.8 μg/ml), respectively) (ALK-ABELLO, Spain). The early response was scored as the wheal diameter 15 minutes after challenge. The reaction on histamine phosphate solution and phosphate buffer diluent served as positive and negative controls.

Atopy patch test
The atopy patch test (APT) was performed as previously described.[2;10;24]
Clinically non-involved skin of the back was stripped 10 times with adhesive tape after which Der p1 (0.1 ml aqueous extract, 10,000 AU/ml, HAL, Haarlem, the Netherlands) was applied using Leucotest patches (Beiersdorf AG, Hamburg, Germany). APT were read after 24 hours. APT were scored 0: no reaction present; 1+: erythema and induration present; 2+: erythema and papules present and 3+: erythema, papules and vesicles present.

Statistical Analysis
All statistical tests were performed with SPSS 10.0 as two-tailed tests. The normal distribution of the variables were checked with the Kolmagorov-Smirnov test. The Wilcoxon matched-pairs signed rank test (WMP-test) and the paired samples t-test were used for analysis within groups and the Mann-Whitney U-test (MWU-test) and the two-sample t-test between groups.

Results

Eighty-six patients with AD were included, 41 were randomly allocated to the placebo group and 45 patients to the active treatment group. Two patients dropped out before four months, one due to moving to another house and the other found the study too strainfull. Six other patients dropped out after four and before twelve months. Two due to pregnancy, one found the mattress encasing too hot causing increased sweating resulting in an increase of AD, one due to regularly using class 3 topical steroids, one due to moving to another house and one because of unknown reasons. Seventy-seven patients completed the study. Four patients were excluded because their dustsamples were not complete (figure I). The general characteristics of the study population are presented in table II. The patients were characterised by their allergic symptoms, like AD (AD), allergic rhinitis (AR) and allergic asthma (AA).

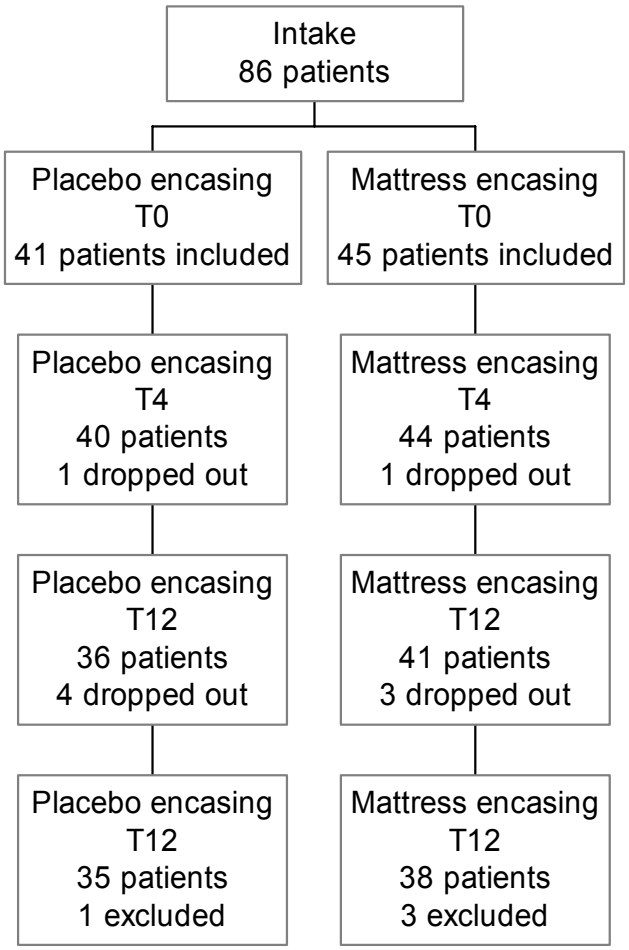

Figure I: Inclusion, exclusion and dropping out of patients who were randomly allocated among both groups..

Table II: General characteristics of the population

	Placebo	**Active treatment**
Age ($\bar{x}$, s) in years	26.2 ± 10.7	24.2 ± 10.36
AD (n)	2	6
AD + AR (n)	13	14
AD + AA (n)	3	2
AD + AA + AR (n)	17	16
Gender (m:f)	14:21	13:25
LSS severity (median, range)	14 (6-53)	17 (6-60)
LSS extent % (median, range)	26 (2-87)	19.5 (3-88)
Total patients	35	38

AD=Atopic Dermatitis
AA=Allergic Asthma
AR=Allergic Rhinitis

Dust outcome measures in the mattress

In the active treatment group a significant decrease was seen in Der p1 and Der p1 + f1 between T0 and T12 and also for Der p1 +f1 between T0 and T4 in the mattress (table III). The change in dust weight in the mattress was not significant. The treatment induced proportional change for Der p1 + f1 was significant higher in the active treatment group compared with the placebo group but not for Der p1 alone (figure II). The proportional significant change of Der p1 + f1 (log difference between T0 and T12) was chosen as a primary outcome measure for effect of Goretex encasings. Meaning that the difference in Der p1 + f1 between T12 and T0 was significantly lower in the Goretex group compared to the placebo group in the between groups analysis.

Dust outcome measures in the bedroom and livingroom

Also in the active treatment group a significant decrease in Der p1 and Der p1 +f1 between T0 and T12 was seen in the bedroom. At starting point there was a significant higher concentration of Der p1 + f1 in the bedroom of the placebo group compared with the active treatment group (table III), this was not caused by a difference in floor covering between both groups (table VI). No significant change was seen in the dust weight in the bedroom and living room(data not shown). In the placebo group there was no significant change in Der p1 and Der p1 + f1 (table III). The treatment induced change for Der p1 + f1 was also significant in the bedroom but not in the livingroom and not for Der p1 alone (figure II).

Primary and secondary outcomes

The LSS severity and extent, VAS itch and specific anti-Der p1 IgE in the active treatment group at T12 compared to T0 were significant lower, also the anti-Der p1 IgE in the placebo encasing group was at T12 significantly lower compared to starting point.

Table III: Effect of placebo and active treatment on Der p1 and Der p1 + Der f1 allergen in ng/g dust.

	T0 placebo	**T12 placebo**	**T0 active treatment**	**T4 active treatment**	**T12 active treatment**
Dust outcome measures					
Mattress (geometric mean, 95 % CI)					
Der p1	841 (494-1432)	679 (339-1360)	945 (555-1609)[*1]	545 (198-1498)	446 (271-735)[*1]
Der p1 + Der f1	3388 (1913-6000)	3749 (1921-7315)	4069 (2573-6437)[*2,3]	1675 (938-2989)[*2]	1319 (851-2046)[*3]
Bedroom					
Der p1	542 (248-1076)	402 (203-798)	1171 (595-2302)[*4]	499 (156-1598)	609 (335-1106)[*4]
Der p1 + Der f1	1539 (771-3070)[*8]	2220 (1235-3994)	4498 (2752-7352)[*5,6,8]	1491 (624-3564)[*5]	2098 (1269-3469)[*6]
Livingroom					
Der p1	979 (339-1360)[*7]	298 (157-570)[*7]	654 (344-1244)	494 (150-1632)	584 (326-1043)
Der p1 + Der f1	1114 (600-2067)	966 (509-1831)	1277 (676-2416)	1388 (648-2971)	1308 (735-2327)

T-test
1 p=0.007 comparing T0 with T4 in the active treatment group.
2 p=0.009 comparing T0 with T12 in the active treatment group.
3 p=0.005 comparing T0 with T12 in the active treatment group.
4 p=0.019 comparing T0 with T12 in the active treatment group.
5 p=0.011 comparing T0 with T4 in the active treatment group.
6 p=0.007 comparing T0 with T12 in the active treatment group.
7 p=0.045 comparing T0 with T12 in the placebo group.
8 p=0.011 comparing T0 between the placebo and active treatment group

Table IV: Effect of placebo and active treatment on primary and secondary outcome measures if not otherwise stated median and range are given.

	T0 placebo	**T12 placebo**	**T0 active treatment**	**T4 active treatment**	**T12 active treatment**
LSS severity	14 (6-53)	15 (0-68)	17 (6-60)*1,2	10 (0-51)*1	13 (0-55)*2
LSS extent %	26 (2-86)	21 (0-75)	19.5 (3-88)*3	16.5 (0-99)	14.5 (0-87)*3
VAS itch (mm)	66.5 (0-100)	60 (0-100)	73.5 (0-100)*4	67 (3-100)	63 (4-100)*4
VAS sleeplessness (mm)	8.5 (0-69)	4 (0-83)	14 (0-100)	13 (0-87)	10 (0-90)
IDT (mm) ($\bar{x}$, s)	14 ± 6.8	13.5 ± 6.1	11.6 ± 6.3	12.3 ± 7.5	12.7 ± 7.6
APT 24 h	1 (0-3)	1 (0-2)	1 (0-2)	n.d.	1 (0-2)
Total serum IgE (kU/L)	721 (26-7400)	819 (22-18400)	559 (63-25200)	n.d.	421 (39-20500)
Specific IgE (anti Der p1)	39 (0.3-90)*5	30.9 (0.2-90)*5	27.3 (0.2-90)*6	n.d.	25.8 (0.2-88.3)*6
Total blood eosinophils (10^6/L)	350 (10-2200)	295 (0.7-1640)	410 (20-1700)	n.d.	340 (50-1120)

n.d. = not done

Wiloxon Matched Pairs Test
1 p=0.010 comparing T0 with T4 in the active treatment group.
2 p=0.017 comparing T0 with T12 in the active treatment group.
3 p=0.038 comparing T0 with T12 in the active treatment group.
4 p=0.045 comparing T0 with T12 in the active treatment group.
5 p=0.025 comparing T0 with T12 in the placebo group.
6 p=0.013 comparing T0 with T12 in the active treatment group

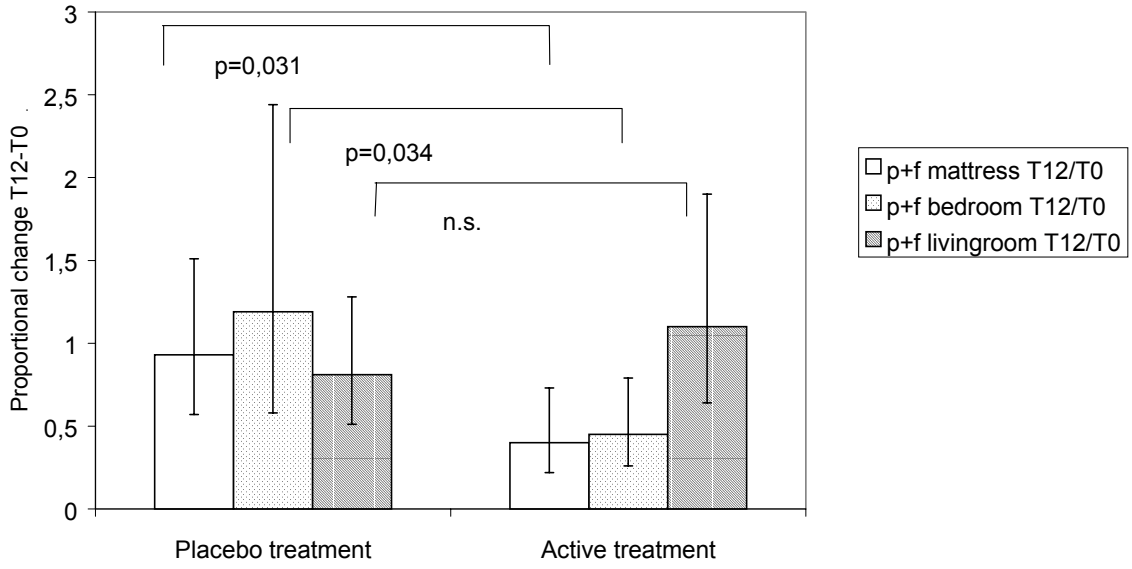

Figure II: Der p1 + Der f1 at twelve months in proportion to starting point.

The VAS sleeplessness, IDT, APT, total serum IgE, total blood eosinophils did not significantly change. The change in LSS severity, extent and VAS itch was not statistically different between the placebo and encasing groups as were the other secondary outcomes (table IV and V). Table VI shows the distribution of floor covering within our study group, surprisingly 40 % of the patients in both groups with HDM allergy and AD have carpet covering in the bedroom. Despite advises concerning measures to lower the domestic HDM level which most of them must have received in the past.

Table V: Difference (T12-T0) of placebo and active treatment on primary and secondary outcome measures if not otherwise stated median and range are given.

	Placebo encasing group	**Active treatment group**
LSS severity	- 2 (-22-28)	- 4 (-26-29)
LSS extent %	-4 (-45-33)	- 3.5 (-51-39)
VAS itch (mm)	- 8.5 (-89-77)	- 4 (-90-71)
VAS sleeplessness (mm)	0 (-56-83)	0 (-75-64)
IDT (mm) ($\bar{x}$, s)	- 0.5 ± 4.8	0.73 ± 4.6
APT 24 h	0 (-1-1)	0 (-2-2)
Total serum IgE (kU/L)	-11 (-2200-16330)	- 7 (-4700-1400)
Specific IgE (anti Der p1)	- 2.15 (-58.5-44.6)	- 2.15 (-30.2-33.9)
Total blood eosinophils (10^6/L)	10 (-560-480)	-40 (-660-400)

*There were no significant treatment induced changes between the two groups

Table VI: Distribution of floor covering

	Placebo encasing group %	Active treatment group %
Bedroom		
Smooth	53	58
Smooth + rug	0	3
Carpet	47	39
Livingroom		
Smooth	57	50
Smooth + rug	26	21
Carpet	17	29

Discussion

In this double-blind randomised placebo controlled study with AD patients, the effect of Goratex (n=38) and placebo encasings (n=35) was studied. The LSS severity and extent score were used as primary outcome measures. The secondary outcome measures were VAS itch and sleeplessness; the intradermal test and the APT with Der p1; total serum IgE; specific IgE against Der p1 and total blood eosinophils. Regarding the primary outcome measures, the decrease of LSS extent and severity of T12 compared to starting point between the placebo and the Goratex encasings was not statistically significant. Goratex encasings did not result in an improvement of AD compared with placebo encasings. The treatment induced change of secondary outcome measures between the groups did not improve either. In scientific literature treatment effects of avoidance measures were either compared to baseline levels or between different treatment groups, this resulted in different significant and not significant outcomes. In our opinion, in the evaluation of HDM avoidance treatment effects there should be a significant decrease in HDM allergens between placebo and active treatment groups, because a significant improvement in placebo and treatment groups does not necessarily mean that the treatment effect is causing the improvement. The study itself should at least last 12 months to avoid seasonal effects.

In 1996 Tan et al. published a double-blind controlled trial with 60 AD patients. The active housedust-mite allergen avoidance treatment consisted of Goretex-covered mattresses, benzyltannate spray and a high-filtration vacuum cleaner in bed and livingroom during six months. The active group showed a drastic decrease in mattress dust weight with time. Both placebo and active treatment reduced significantly the Der P1 concentration in bed and livingroom in 6 months. Although both study groups showed significant reductions in the severity and area affected by AD, the change in the AD severity score was significantly higher in the active group (p=0.008) than in the placebo group.[18] More recently a new placebo-controlled trial of twelve months duration was published.[25] The authors of the recent study included 40 patients, 11 were unsensitized to HDM. They concluded that in their study the HDM exposure (2 patients in the placebo group, 6 patients in the active treatment group) and the eczema severity (18 patients in the placebo group, 22 patients in the active treatment group) was significantly reduced. Regarding the inclusion criteria and the number of patients used for analysis, the effect of mattress encasings is not as clear as the authors stated. Lack of improvement of AD in a double-blind placebo-controlled study of housedust-mite avoidance

measures with only 10 AD patients in two treatment groups was recently described.[26] The low power of this study could still account for the lack of statistical significant difference between the two groups.

Lack of clinical efficacy might also be due to a low baseline level of clinical AD. In comparison to the data of Tan[18] and et al. the median score of severity seems almost in the same range (median score 15-30), although the extent of AD in our study is somewhat less. Tan observed a decrease in the extent and severity of AD in control and verum groups. Since their patients were studied for six months this could have been due to seasonal effects. For that reason in our study patients were followed for 12 months.

Lack of effect in the present study might be due to a low baseline concentration of Der p1 resulting in a little change of Der p1 after intervention. Some authors reported higher amounts of Der p1 per gram fine dust (geometric mean 20-40 mcg/g) and stated that it might be the mean level of der p1 allergen concentration for temperate climates without any intervention.[27-32]Others reported lower levels of Der p1 (geometric mean 400-10000 ng/g) in temperate climates.[33-37] However, our baseline data Der p1 in the mattress (841 and 945 ng/g dust, placebo and active treatment group receptively) has the same mean concentration as earlier reported by Cloosterman et al.[38] So this lower concentration of Der p1 per gram dust might be representative for the Dutch population. Some high altitude studies reported lower geometric means for Der p1 + Der f1 of 360 ng/g dust and 180 ng/g dust for Der p1 in mattresses.[39;40] There seems to be some room for improvement left in the active treatment group in this study (the median Der p1 concentration in the mattress after twelve months intervention in our study was 446 ng/g dust and the Der p1 + f1 concentration was 1319 ng/g dust), but it is doubtful if mattress encasings alone can decrease the concentration of Der p1 + Der f1 to this extent.

We tried to isolate the groups who would benefit most and divided the groups in low and high (below and above geometric mean) Der p1 exposure and a low and high (below and above median severity and extent) AD score. No significant difference in effect between these subgroups were seen (data not shown).
Another reason why the decrease in allergen exposure did not result in clinical improvement might be that the sleeping period in which the decrease in concentration of Der p1 or Der p1 + Der f1 in mattress and bedroom is experienced could be too short. Patients might still be exposed to higher HDM levels outside the bedroom. Also other allergens in- and outside the domestic environment might have aggravated and maintained AD. Reduction of allergens in other environments (working, school, outdoor) might be equally important to improve AD.

The risk of asthma in children sensitised to cats as compared to those sensitised to mites was much lower in the regions with high mite allergen exposure, but similar in regions with relative low Der p1 levels. Apparently, the presence of mite allergens in homes surpasses the effect of other allergens.[41] The same mechanism might apply to patients with AD. For that

reason the highest treatment effect could be expected from decreasing the concentration of Der p1.

A meta-analysis of house dust mite control measures in the management of asthma performed in 1998 led the authors to the conclusion that current chemical and physical methods aimed at reducing exposure to allergens from house dust mites seemed to be ineffective and that these methods could not be recommended as prophylactic treatment for asthma patients who are sensitive to mites. It was even stated that factors tended to be associated with an overestimation of reported treatment effects.[42]. There are not many studies with AD patients and the use of mattress encasings, therefore a meta-analysis concerning the use of mattress encasings in this group is at this moment not possible.

Conclusively, the odds are evened. Tan's double-blind, randomised placebo controlled study does show improvement of AD when the active treatment group is compared to placebo treatment group. Our double-blind randomised placebo controlled study shows no significant improvement of AD between the two groups. The usefulness of mattress encasings in reducing allergen load is established. However relevant clinically benefit is doubtful.

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Chapter 4

The effect of anti-allergic mattress encasings on house dust mite-induced early and late airway reactions in asthmatic patients.

A double-blind placebo controlled study

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A double-blind placebo controlled study

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Summary

Background: Anti-allergic mattress encasing may provide clinical benefit in asthmatic patients. However, the effect of mattress encasings on allergen-specific parameters, such as bronchial reactions to house dust mite (HDM) challenge, is not clear.

Objective: To investigate the effect of anti-allergic mattress encasings on allergen sensitivity in patients with moderate to severe asthma.

Methods: 27 patients with asthma and house dust mite allergy were studied in a double blind, placebo controlled study. Concentrations of Dermatophagoides pteronyssinus (Der p1) were measured in mattress dust before and after 1 year of treatment; bronchial histamine challenge, bronchial challenge with HDM and intradermal skin challenges with HDM were performed. The number of eosinophils in peripheral blood was assessed.

Results: In the active group, but not in the placebo group there was a significant reduction in Der p1 concentration in the dust collected from the mattresses after 1 year of treatment compared to before. There was a significant difference between the groups with respect to HDM-induced early reaction in the airways (ER) and number of blood eosinophils, which reflected an increase in ER and eosinophils in the placebo group without significant change in the active group. No significant improvement in PC_{20} histamine, late reaction (LR) and skintests was found in both groups.

Conclusion: Our data suggest that encasings protect against a further increase in allergen sensitivity in asthmatic patients, so their use should be recommended.

Keywords: mattress encasings, allergic asthma, house dust mite, bronchial allergen challenge.

Abbreviations

Der p1:	Dermatophagoides pteronyssinus
ER:	Early asthmatic reaction
LR;	Late asthmatic reaction
HDM:	House dust mite
BR:	Histamine-induced bronchial responsiveness
FEV_1:	Forced expiratory volume in 1 second
VC:	Vital capacity
PC_{20} histamine:	Provocative concentration of histamine resulting in a 20% fall of FEV_1
PD_{20} allergen:	Cumulative dose of allergen resulting in a 20% fall of FEV_1
BU:	Biological Units

Introduction

Over the last decades, the prevalence and incidence of asthma have increased despite improved medical treatment. One of the contributing factors for this increase is thought to be exposure to allergens. House dust mite (HDM) has been proven to be one of the most important allergens. An association exists between the level of HDM exposure and the risk to develop asthma[1-3], i.e. the higher the exposure the higher the risk. Moreover, avoidance of HDM, as can be reached in the mountains or during hospitalisation, can result in an improvement of asthma symptoms, peak flow values, non-specific hyperresponsiveness and the use of medication.[4-6]

Allergen avoidance is the first step in the treatment of patients with allergic asthma. Several procedures have been developed to limit the exposure to HDM. Most procedures are expensive, require active participation of the patients and have not been extensively studied in double blind, placebo-controlled studies. One such allergen avoidance measure is the application of encasings. Mattresses, pillows and bedding often contain large amounts of HDM, resulting in high exposure for several hours during the night. The use of specific anti-allergic mattress encasings can result in a strong reduction of Der P1 levels on top of the mattress[7-9], with subsequent clinical improvement and a reduction in histamine-induced bronchial responsiveness in asthmatic patients.[7;9] These studies, however, have been generally performed in relatively mild asthmatics. In addition, there are no data on allergen-specific parameters, such as bronchial reactions to house dust mite challenge.

In the present study the effect of anti-allergic encasings was studied on bronchial response upon challenge with allergen as well as histamine in patients with moderate to severe asthma in a double-blind placebo controlled design. In addition other allergic parameters were studied, such as skin responsiveness to house dust mite, peripheral blood eosinophils and specific IgE to HDM.

Methods

Patients

Twenty-seven atopic, non smoking patients with asthma and house dust mite allergy (10 females and 17 males, age 11-51 years) participated in the study. The clinical data are presented in Table 1. Although most patients had moderate to severe asthma, 3 patients in each group did not regularly use inhaled steroids. The patients were selected for increased bronchial responsiveness to histamine inhalation (PC_{20} < 4 mg/ml, 30 seconds inhalation of histamine phosphate solution), positive skin tests and/or elevated specific IgE to HDM allergen, early bronchial reaction to HDM inhalation and relevant HDM exposure on the mattress (> 1 µg Der P1/ g dust). All patients had FEV_1 values > 60 % (predicted value). Pollen allergic patients were included and evaluated outside the pollen season. Patients did not have a history of respiratory tract infections in the previous six weeks or severe asthmatic attacks in the previous six months. Patients having a furred pet were only admitted when they had no pet allergy. None had received oral corticosteroids in the previous 6 months. All patients gave informed consent. The Medical Ethical Committee of Asthma Centre Heideheuvel, the Netherlands, approved the study.

Study design

The study was performed in a randomised placebo-controlled, double blind, parallel group design, comparing the effect of allergen-impermeable encasings on the mattresses, pillows and comforters during one year with matching placebo encasings. At the start of the study a trained respiratory nurse visited the houses of the patients in order to establish allergen avoidance measures already present. All patients included in the study had bedroom floors without carpets. Patients were instructed to wash their sheets each week at 60°C. Apart from the mattress, pillow and comforter encasings no other allergen avoidance measures were taken. At the end of the study the nurse visited the houses again to verify that no other changes were made to the bedroom during the study. The patients were included continuously; the inclusion period lasted 2 years.

At the first visit patients underwent clinical evaluation. FEV_1 and VC values were measured, skin tests were performed and a PC_{20} histamine was assessed. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate one week before the challenge, theophyllines, oral ß $_2$- adrenergic drugs, long-acting inhaled ß $_2$-adrenergic drugs and antihistamines 48 hours before the tests and inhaled ß $_2$-adrenergic drugs six hours before the tests. The patients continued their regular medication after the tests. The patients were told not to change their medication during the intervention period and to record their medication use in an asthma diary.

Seventy-two hours after the bronchial histamine challenge the patients were admitted to the hospital for three consecutive days. On the first day, starting at 9.00 AM, a challenge with a diluent control was performed. The second day, at 9.00 AM, subjects underwent allergen challenge with HDM. Before the challenge blood sampling was performed for eosinophil counts. Spirometry was performed as on the first day. At the third day patients underwent a second histamine provocation.

Dust was collected from the mattresses of the patients for Der P1 measurement before installing the encasings. After 1 year the same test procedure was repeated and dust was collected on top of the mattress cover.

Collection of dust

Before and at the end of the intervention, mattress dust was collected by a trained respiratory nurse using a vacuum cleaning apparatus (Philips type Vitall 377, 1300 watt the Netherlands). She vacuum cleaned the whole mattress during 2 minutes with a special filter device (Petersen-Bach A/S, Denmark, mean pore size 5-6 µm, maximum pore size 10 µm). At the start of the study dust was collected directly from the mattress; at the end of the study dust was collected on top of the encasing**,** using always the same vacuum cleaner. The filters were stored in the freezer (-20°C) until analysis at the end of the study.

Der p1 Analysis

After sieving (0.35 mm), the amount of fine dust was weighed and a 10 % (wt/vol) extraction in 0.01 mol/L NH_4HCO_3 buffer was performed by overnight rotation at 4^0 C. The samples were centrifuged and the supernatants were used for the measurement of Der p1 concentration. Der p1 antigen was measured using an enzyme-linked immunosorbent assay

(ELISA). Monoclonal antibodies (ALK, Horsholm, Denmark) against Der p1 were immobilised on a 96-well plate. The incubation with the dust extracts was followed by a second incubation step with a polyclonal antibody (horseradish-peroxidase). After adding 1,2 phenyldiamine HCL (OPD) as substrate the absorption at 490 nm was measured using an ELISA reader.

Histamine challenge

Histamine phosphate solutions (doubling concentrations from 0.25 to 32 mg/ml) were administered through a De Vilbiss 646 nebulizer with a gauged output of 0.13 mg/ml. The nebulizer was mounted to a valvebox containing an aerosol filter. The nebulation time was 30 seconds, during which the patient was instructed to breathe quietly. The test started with inhalation of a phosphate buffer aerosol. Prior to the inhalation three measurements of VC and FEV_1 were performed (Jaeger Masterscreen)**.** FEV_1 was measured after each doubling concentration. The PC_{20} histamine was derived by linear interpolation.

Bronchial allergen challenge.

Allergen solutions were prepared from stock solutions of *Dermatophagoides pteronyssinus* in PBS supplemented with 0.03 % human serum albumin and 0.5 % phenol (SQ 503, ALK Benelux). Fivefold increasing concentrations of allergen solutions were prepared ranging from 80 to 10,000 BU/ml. The allergen solutions were administered through a De Vilbiss nebulizer mounted to a valvebox containing an aerosol filter (output 0.13 mg/ml). The patients were instructed to breathe normally during one minute for each dose. Increasing doses were given at 15 minutes intervals. The challenge procedure was terminated when the FEV_1 value fell >15 % below the baseline value. After the last inhalation FEV_1 was recorded at 10 minutes intervals for the first hour, to determine the early asthmatic response and at one-hour intervals thereafter until 10 hours after the last inhalation, to determine the late asthmatic response. FEV_1 values were corrected for diurnal variation, determined during the previous day. The cumulative provocation dose of allergen necessary to induce a fall in FEV_1 value > 20% from baseline (PD_{20} allergen) was calculated. This PD_{20} allergen is based on the observed maximal fall of FEV_1 and the delivered dose of allergen and characterises the severity of the early and late asthmatic response.[10;11]

Skin tests

Intradermal challenges (30 BU/ml, 0.03 ml) were performed on the back of the patients with a standardised HDM extract (ALK Benelux, SQ-503). The early response was scored as the wheal diameter 15 minutes after challenge. Late responses were measured 6 hours after challenge: indurations were determined according to a procedure suggested by Sokal.[12] The reactions on histamine and phosphate buffer diluent served as positive and negative controls.

Peripheral blood eosinophils

A blood sample was taken at 9.00 AM at the start of the study and after 1 year.
Blood eosinophils were counted using Bürker-Turk counting chamber.

Mattress encasings

In the active group, mattresses, pillows and bedding were encased using ACb^{TM} Allergy Control covers supplied by Cara C'air (Velserbroek, The Netherlands)**.** The same company made the matched placebo covers. The encasings were placed in position by a research nurse and left in situ during 1 year. The patients were advised to use their normal sheets on top of the mattress, pillow and comforter encasings and use no other additional bedding.

Data analysis

Statistical analyses were performed with SPSS 9.0 standard version. Comparisons within groups (before and after intervention) were made with the Wilcoxon signed rank test (WSR). Mann Whitney U test was used for between group comparisons. P values less than 0.05 were considered significant. Data were log-transformed to obtain normal distribution, if necessary. The log-transformed data were analysed, using the sign test. These log-transformed values were expressed as mean value $\pm$ standard error of the mean (SEM).

Results

Demographic characteristics were similar between the two treatment groups (table 1)**.** There were no significant differences between the two groups with regard to Der p1 concentrations, PC_{20} histamine, PD_{20} allergen, skin tests, blood eosinophils, skin tests to house dust mite and medication use. Analyses of the diary cards at 0, 4, 8, 12 months showed that there was no change in medication during the study in both groups.

Table 1: Clinical data of the patients

Patient	age	sex	FEV1 (% pred.)	PC20 hist (mg/ml)	skin test*	rhinitis	medication asthma	medication rhinitis
Placebo								
1	21	M	97	1.76	2.1	-	B, SB	-
2	11	M	79	0.74	1.1	+	B, SB	-
3	19	F	111	1.00	1.4	+	SB	-
4	11	M	97	4.00	1.4	+	B,SB	-
5	29	M	81	0.33	1.2	-	F, SM	-
6	21	M	73	2.43	2.0	+	B,SB	B
7	27	F	70	0.90	1.2	+	B,SB	B
8	44	M	70	1.89	1.2	+	F, SM	F
9	17	F	138	1.78	1.9	+	-	B
10	40	M	64	1.13	1.6	+	B,SB	-
11	29	M	103	0.71	1.5	+	-	-
12	28	F	73	0.45	2.2	-	F, SB	-
13	12	M	106	4.00	1.6	+	B,SB	-
mean	24		89	1.62	1.6			
s.d.	10		21	1.22	0.4			
Active								
1	25	F	99	1.19	1.5	+	B,SB	-
2	29	M	99	0.95	1.6	-	B	-
3	41	M	67	3.79	2.2	+	B, SB	-
4	24	F	86	2.00	1.8	+	B, SB	-
5	31	M	81	1.22	1.5	-	-	-
6	24	M	80	0.55	1.1	+	B, SB	B
7	15	M	86	0.65	1.7	-	F	
8	22	F	104	2.67	1.4	+	B	-
9	51	F	70	0.45	1.2	+	B, SB	B
10	32	M	68	0.42	1.1	-	B, SM	-
11	36	F	103	0.35	1.8	+	SB	B
12	13	M	79	2.45	2.6	+	SB	-
13	42	M	75	0.42	1.2	-	B, SM	-
14	18	F	103	2.35	1.2	+	F, SM	F
mean	29		86	1.39	1.6			
s.d.	11		14	1.08	0.4			

(*) = X times histamine reaction

B beclomethasone or budesonide; F fluticasone: SB salbutamol

SM salmeterol; FO formeterol

s.d. = standard deviation

Der p1 concentrations on mattresses

Figure 1 shows geometric mean Der p1 concentrations on the mattresses before and 12 months after the start of the study in both groups. Der p1 concentrations on the mattresses were significantly lower in the active group after 1 year (16.2 +/- 6 and 2.2 +/- 0.9 microgram Der p1/g fine dust, respectively; p=0.002). In the placebo group, there was no significant reduction in Der p1 (26.4 +/- 11.7 and 27.0 +/- 12.8 microgram Der p1/g fine dust, respectively; p=0.58). There was a significant difference in the treatment-induced change in Der p1 concentration between the two groups (p=0.04).

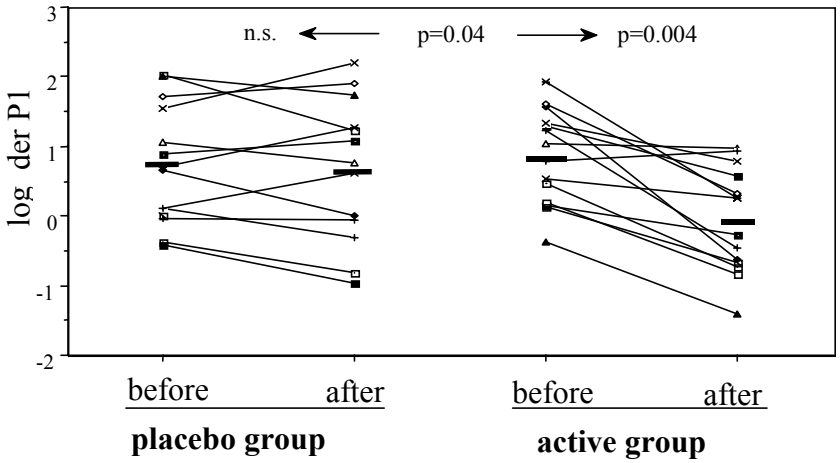

Figure 1: Der p1 concentrations on top of the mattress before and after 1 year of intervention : mean value (log data) of the groups is represented (Active: 0.85 and 0.06 µg Der p1/g dust respectively. Placebo: 0.77 and 0.66 µg Der p1/g dust respectively.) **-** = mean value

Early and late asthmatic responses

In several patients the allergen concentration required to induce a fall in FEV_1 of at least 20% differed during the study. Therefor, the early and late responses on house dust mite challenge were expressed as PD_{20} allergen.

PD_{20} early response

Figure 2a shows the PD_{20} allergen of the early response before and 1 year after the intervention. All patients showed early response before treatment. In the active group, there was no significant change in PD_{20} allergen before and after 1 year (750 +/- 175 BU/ml and 611 +/- 157 BU/ml respectively: p=0.79). In the placebo group, the PD_{20} allergen after 1 year was significantly lower compared to before (PD_{20} 1580 +/- 646 BU/ml and 473 + 161 BU/ml respectively; p=0.003), indicating a more sensitive response after 1 year. There was a significant difference in the treatment-induced change in PD_{20} allergen between the two groups (p=0.04).

PD_{20} late response

Figure 2b shows the PD_{20} allergen of the late response before and one-year after the intervention. Late phase reactions could be demonstrated in 10 patients in the placebo group and in 9 patients in the active group.

There was no significant change in PD_{20} allergen during the year in the active group (PD_{20} 498 +/- 111 BU/ml and 360 +/- 84 BU/ml respectively; p=0.51). In the placebo group there was a significant decrease in PD_{20} allergen after 1 year compared to before (PD_{20} 1103 +/- 385 BU/ml and 394 +/- 144 BU/ml respectively; p=0.002). The treatment-induced change in PD_{20} allergen between the two groups was not significant (p=0.11)

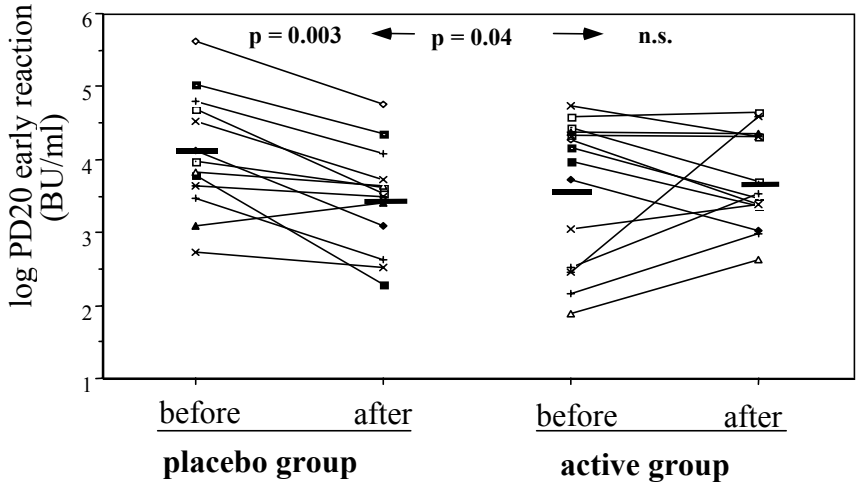

Figure 2a: The effect of mattress encasings on PD_{20} of early asthmatic response; mean value (log data) of the groups is represented (active: 3.62 and 3.69 µg BU/ml respectively. Placebo: 4.10 and 3.47 BU/ml respectively).
n.s = not significant.

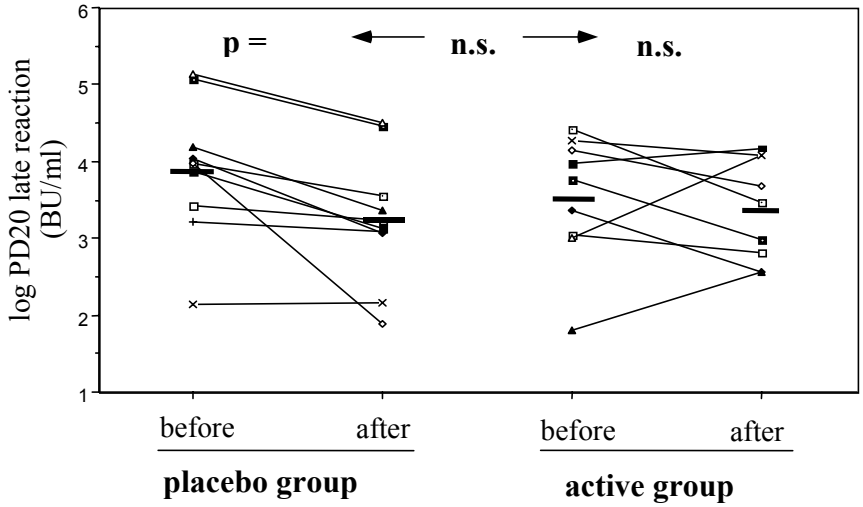

Figure 2b: The effect of mattress encasings on PD_{20} of late asthmatic response; mean value (log data) of the groups is represented (active: 3.53 and 3.38 BU/ml respectively. Placebo: 3.90 and 3.25 BU/ml respectively). Only the results of patients who showed a late phase response are represented.

PC_{20} histamine

Mean log PC_{20} histamine in the active group was 0.24 ± 0.31 mg/ml at the start of the study and 0.32 mg/ml + 0.29 after 1 year, the difference being not significant (p=0.18) (Figure 3). In the placebo group, there was no significant change in PC_{20} histamine during one year (mean log PC_{20} histamine before 0.36 mg/ml ± 0.28; after 1 year 0.39mg/ml ± 0.28: p=1.0). The treatment-induced change in PC_{20} histamine between the two groups was not significant (p=0.77).

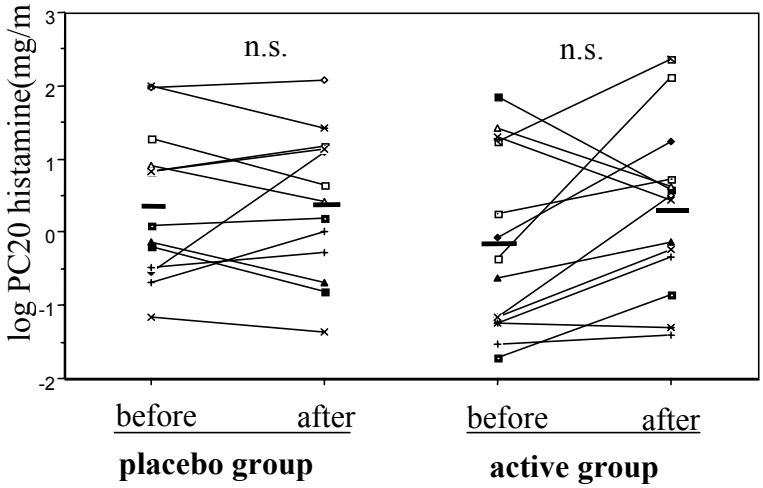

Figure 3: PC_{20} histamine before and after 1 year of intervention; mean value (log data) of the groups is represented, (active: –0.36; 0.44 mg/ml respectively. Placebo: 0.36; 0.39 mg/ml respectively)

Skin reactions

Early reactions

Figure 4a shows the results of the early skin reactions after intradermal allergen challenge before and after 1 year in both groups. There was no significant change in skin reaction during 1 year in the active group (18.5 ± 1.3 mm and 16.1 ± 0.9 mm respectively; p=0.12). This was also the case in the placebo group (18.7 ± 1.8 mm and 17.2 ± 1.8 mm respectively; p=0.58). The treatment-induced change in early skin reaction was not significantly different between the two groups (p=0.66).

Late reactions

There was no significant change in skin reaction over 1 year follow up both in the active group (18.0 ± 2.4 mm and 13.5 ± 2.2 mm respectively; p=0.20) and in the placebo group (12.9 ± 1.9 mm and 13.6 ± 1.2 mm respectively; p=0.58) (figure 4b). The treatment-induced change in early skin reaction was not significantly different (p=0.57) between the two groups.

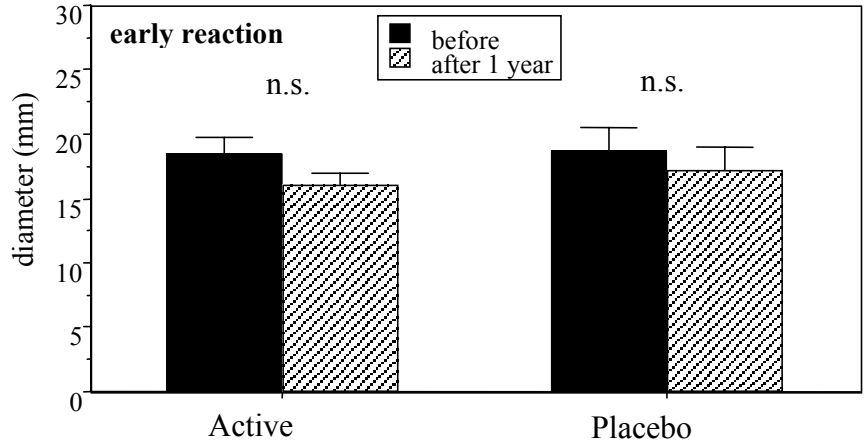

Figure 4a: Early skin reaction before and after 1 year of intervention (mm)

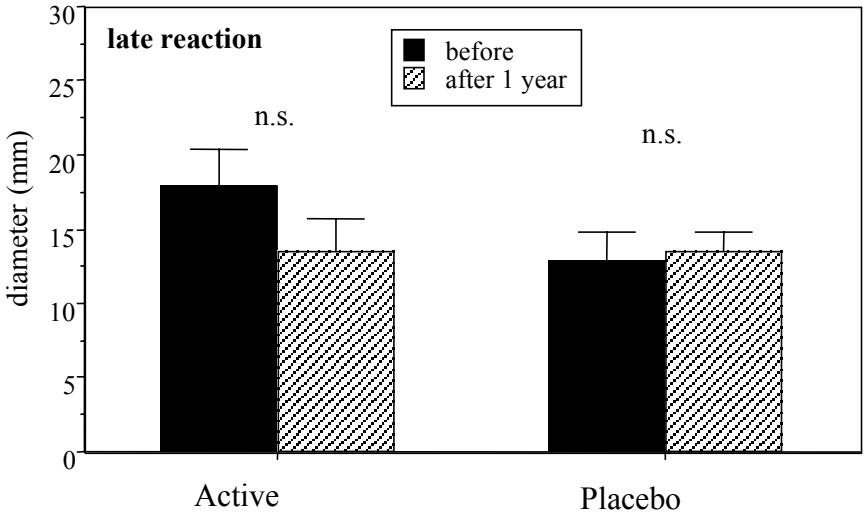

Figure 4b: Late skin reaction before and after 1 year of intervention (mm)

Specific IgE

There was no significant change in the level of specific IgE after 1 year compared to before in the active group (54.1 $\pm$ 10.1 PRU/ml and 44.3 $\pm$ 10.4 PRU/ml respectively; p=0.13), neither in the placebo group (59.2 $\pm$ 112.6 PRU/ml and 53.3 $\pm$ 10.0 PRU/ml respectively; p=0.20). The treatment-induced change in specific IgE was not significantly different (p=0.93) between the two groups.

Peripheral blood eosinophils

Total blood eosinophil counts did not significantly change after one-year in the active group (382 $\pm$ 47 x10^6/l and 366 $\pm$ 50 x10^6/l respectively; p=0.66). In the placebo group total blood eosinophil counts were significantly higher after 1 year compared to before (273 $\pm$ 37 x10^6/l and 436 $\pm$ 69 x10^6/l respectively; p=0.03). There was a significant difference in the treatment- induced change in number of blood eosinophils ($p < 0.05$)(Figure 5).

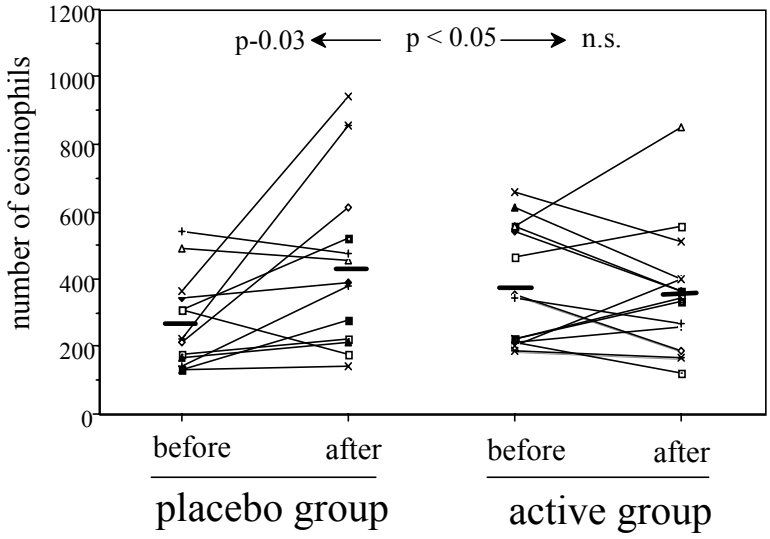

Figure 5: The effect of mattress encasings on the number of peripheral blood eosinophils (10^6/l)

Discussion

The present study was performed in order to investigate the effect of anti-allergic mattress encasings on allergen sensitivity in patients with moderate to severe asthma and house dust mite allergy. We found a significant reduction in Der p1 concentrations in the dust collected from the mattresses in the active group, which was also significantly different from the placebo group. There was a significant difference in early response (ER) to allergen and number of peripheral blood eosinophils between the active and the placebo group. This difference reflected increases in ER and number of eosinophils in the placebo group, whereas no change occurred in the treatment group. No significant differences between the groups occurred with respect to PC_{20} histamine, late bronchial reaction, skin test responsiveness and specific IgE.

It has been demonstrated that higher exposure to HDM is associated with more severe asthma.[13-16] In an attempt to maximally reduce the HDM exposure at home, several combinations of avoidance measures have been studied.[6;17-22] These studies are difficult to compare, because of the large differences in applied avoidance measures (often combination of chemical and physical methods), outcome parameters, study population and design.

In the Netherlands, mattresses and bedding are a major source of HDM and the use of anti-allergic encasings has become a more or less standard procedure in the treatment of HDM-allergic asthmatic patients. Therefore, we have chosen to focus solely on the additional effect of mattress, pillow and bedding encasings, leaving other allergen avoidance measures unchanged. In addition we have chosen to investigate a population of patients with severe bronchial hyperresponsiveness despite the use of inhaled bronchial corticosteroids.

In our study we found a significant reduction in Der p1 concentrations on the mattresses in the active group after 1 year of intervention. The placebo encasings used in the study had a similar appearance as the active encasings, but did not protect against allergen exposure, as Der p1 concentrations remained the same after 1 year. We have chosen 1 year of intervention to exclude seasonal variations in Der p1 exposure, because seasonal variation in mite levels may easily exceed a factor of two or three when winters are relatively cold.[15;23]

Some earlier studies using several different types of mattress encasings have also shown a reduction of Der p1 exposure on top of the mattress.[7-9;24;25] Van der Heide et al.[9] showed the decrease in Der p1 on the mattresses to be greater with mattress encasing than with acaricide treatment. In contrast, when combining impermeable covers over mattress, pillows and duvet with tannic acid/acaricidal spray on the carpets and furniture, Marks et al found a 29% reduction in HDM allergen levels on the beds after two weeks but after 3 and 6 months the reduction in Der p1 concentrations was not significant anymore.[19] The authors suggested that in a high HDM environment simple chemical treatment and encasement of bedding is not sufficient to cause a sustained beneficial reduction in allergen levels. Our study was performed in a high HDM environment as measured by Der p1 concentrations on the mattress and showed a significant reduction in HDM. The difference between the studies is the presence of carpets on the floors in Mark' study and the absence in our study. The above data combined suggest that encasings are effective in HDM reduction, provided that carpeting is avoided.

In the present study the significant reduction in Der p1 exposure in the active group was not associated with significant effects on histamine-induced hyperresponsiveness. Other studies showed variable results with respect to effects on hyperresponsiveness.[8;9;19;20;25-30] This may be due to duration of use and effect of encasings; the study population duration seems not essential since both short term (12 weeks - 6 months[20;22] and long-term studies[9] have shown beneficial effects. The severity of asthma may have affected the outcome of the studies. Studies with a positive effect concerned patients with mild to moderate asthma.[3;7] For instance van der Heide et al.[9] included patients with a PC_{20} < 32 mg/ml (mean value 3.82 mg/ml), we included patients with severe hyperresponsiveness (PC_{20} < 4 mg/ml, mean value 1.39 mg/ml). Finally, mattress encasings reduce HDM exposure during the night, yet patients may still be exposed to relatively large amounts of HDM from other sources during the day. All studies sofar did not measure these confounding factors. In addition, the severity of hyperresponsiveness is also determined by other factors such as other allergens, viruses and air pollution, which are not influenced by the avoidance measures. Especially, in patients with more severe asthma the relative contribution of the night-time HDM exposure on the level of hyperresponsivenes may be limited.

We evaluated effects of allergen avoidance on allergen-specific parameters in the airways, skin and peripheral blood. We did not find effects on early and late skin reaction to HDM nor on HDM-specific IgE in peripheral blood after 1 year of intervention. This is compatible with

the data of Wickman et al. who also found no change in the degree of allergen sensitisation assessed by skin prick tests or specific IgE antibodies against Der p1 of Der f1 after 18 months of HDM-avoidance measures including mattress encasings.[31] Other studies also showed that the use of mattress encasings did not reduce total IgE, allergen-specific IgE or skin test sensitivity to HDM, despite the reduced HDM exposure.[9;32]
Our study is to our knowledge the first to evaluate effects of mattress encasings on allergen sensitivity in the airways. We could not demonstrate an increase in PD_{20} allergen, both in the early and late response after bronchial challenge with HDM, in the active group. In the placebo group, however, both ER and LR PD_{20} allergen, significantly decreased after 1 year compared to before, indicating an increase in allergen sensitivity. The difference between the groups was significant for the ER. This finding is difficult to explain. An increase in allergen exposure or an increase in hyperresponsiveness can not explain the increased allergen sensitivity, because these parameters did not change in the placebo group. Changes in PD_{20} cannot be explained by changes in PC_{20} histamine alone.[33] Furthermore, the use of medication was unchanged in both study groups. The only parameter that changed during the study was Der p1 exposure, which was significantly reduced on the beds of the patients in the active group. This might suggest that a reduction in Der p1 exposure after the use of the anti-allergic mattress encasings might prevent a further deterioration in lower airway allergen sensitivity, as seen in the placebo group.
Another surprising finding was the significant increase in the number of peripheral blood eosinophils in the placebo group after 1 year that was not seen in the active group. Also this difference between the groups can only be explained by differences in allergen exposure. The significant increase in blood eosinophilia in the placebo group was associated with an increase in airway allergen sensitivity, but not with an increase in hyperresponsiveness. This latter finding is in contrast with other studies showing a positive correlation between blood eosinophilia and hyperresponsiveness[34], though in a cross-sectional way.

The present study showed that the use of anti-allergic mattress encasings in patients with moderate to severe asthma did not result in a reduction in hyperresponsiveness or airway allergen sensitivity, despite a significant reduction in Der p1 exposure. It is possible that the limited efficacy is due to the severity of asthma in our study population. Since our data suggest that there is some protective effect against further increase in airway allergen sensitivity, the use of anti-allergic mattress encasings in this population should still be recommended.

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Chapter 5

Clinical evaluation of the effect of anti-allergic mattress encasings in patients with moderate to severe asthma and house dust mite allergy

A randomised double blind placebo controlled study

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Clinical evaluation of the effect of anti-allergic mattress encasings in patients with moderate to severe asthma and house dust mite allergy

A randomised double blind placebo controlled study

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Abstract

Background: The use of anti-allergic mattress encasings in patients with asthma can result in a strong reduction in the level of house dust mite allergen in dust samples. Apart from reduction in histamine induced bronchial hyperresponsiveness, there are few data on the effect of mattress encasings on clinical efficacy and quality of life in patients with moderate to severe asthma.

Methods: 30 patients with asthma and house dust mite allergy were studied in a randomised double-blind, placebo controlled study. Before and after 1 year use of anti-allergic covers, dust was collected from the mattresses to determine concentrations of Dermatophagoides pteronyssinus (Der p1). Bronchial hyperresponsiveness and Quality of Life were measured. The patients scored their symptoms (lungs and nose), morning and evening peakflow values and rescue medication during fourteen days before and after 1 year treatment.

Results: There was a significant reduction in Der p1 concentration in the dust collected from the mattresses in the actively treated group after 1 year of treatment compared to before, no change was found in the placebo group. In both the active and placebo group there was no significant improvement in PC_{20} histamine. Quality of Life improved similarly in both groups. The symptom score of the lower airways did not significantly change in both groups. A significant decrease in nasal symptom score was noticed in the active group compared to before, however there was no significant difference between the groups. No changes in morning and evening peakflow values, peakflow variability, nor in the use of rescue medication were found in both groups.

Conclusion: The use of anti-allergic mattress encasings results in significant reductions in Der p1 concentrations in carpet-free bedrooms. However in patients with moderate to severe asthma airways hyperresponsiveness and clinical parameters are not affected by this effective allergen avoidance.

Keywords: Mattress covers, allergic asthma, clinical evaluation

Abbreviations

Der p1:	Dermatophagoides pteronyssinus
HDM:	House dust mite
BR:	Histamine-induced bronchial reactivity
FEV_1:	Forced expiratory volume in 1 seconds
VC:	Vital Capacity
PC_{20}histamine:	Provocative concentration of histamine resulting in a 20% fall of FEV_1
BU:	Biological Units
PEF:	Peakflow

Introduction

Exposure and sensitisation to house dust mite allergens (HDM) have been established as an important risk factor for the development of asthma in most parts of the world [1] The rate of sensitisation to mite allergens is directly related to its exposure.[2]. The severity of asthma is also related to allergen exposure [3], as measured by the level of bronchial hyperresponsiveness, forced expiratory volume in one second (FEV_1) and variability in peak expiratory flow (PEF). The relation between exposure and asthma symptoms in sensitised patients is complex, but asthma is usually more severe in sensitised patients who are exposed to higher allergen levels [3]. In effectively mite allergen free environments, as in hospitals [4] or in high altitude Alpine sanatoria,[5;6] the condition of asthma patients improves both symptomatically and in terms of non-specific bronchial responsiveness. These results suggest that avoidance of mite allergen lead to a decrease in airway inflammation with consequent improvement in bronchial hyperresponsiveness and symptoms. It may take many months for the clinical effects to become fully apparent and re-exposure often results in a rapid relapse [7]. Thus it is essential to achieve and maintain a major reduction in exposure.

Many methods of allergen avoidance have been tested in small intervention studies, only a few have been subjected to controlled trials. Some show benefit, when reduction in allergen exposure can be reached [8;9], others seem to be ineffective [10;11].
Reduction of allergen exposure in the bedroom is the primary target of avoidance measures, since the bed is the most important habitat and source of mite allergens to which we are exposed for many hours during nocturnal sleep. The most effective and probably most important avoidance measure is to cover the mattress, pillows, and duvets with mite allergen impermeable covers.[8-10] Acaricides have been shown to be ineffective [12], time and energy consuming, and they require repeated application. Carpets are also an important microhabitat for mite colonisation and a possible source from which beds can be reinfested[13], so this source of mites should also be eliminated. Allergen avoidance measures seem to be more effective in an early stage of disease [14]. The question remained what effects avoidance measures have in more advanced stages of asthma.

In the present study we investigated in a double-blind placebo controlled design whether allergen impermeable covers as a single intervention are of clinical benefit to patients with moderate to severe asthma. We included only non-smoking patients with a smooth bedroom floor in stable state of disease for the last 6 months. Patients having a furred pet were admitted when they had no pet allergy. We studied a population of patients with moderate to severe asthma and house dust mite allergy, severe bronchial hyperresponsiveness and a relevant exposition to house dust mite allergens. We choose one year of intervention to exclude seasonal variation in Der p1 exposure [15;16].

Methods

Patients

Thirty eight patients (age range: 11-44 years) with a history of asthma and house dust mite allergy were recruited from the outpatients department of Heideheuvel Asthma Centre in Hilversum, The Netherlands, from January 1996 to December 1998. Informed consent was obtained from the patients or their parents. The patients were selected on the basis of increased bronchial responsiveness to histamine inhalation ($PC_{20} \leq 4$ mg/ml, 30' method), positive skin tests and/or elevated specific IgE to house dust mite allergen and relevant HDM exposition on the mattress (> 1 µg Der p1/ g dust). All patients had FEV_1 values > 60 % (predicted value). Patients did not have a history of respiratory tract infections in the previous six weeks or severe asthma attacks in the previous six months. None had received oral corticosteroids in the previous 6 months. All patients gave informed consent. The Medical Ethics Committee of Asthmacenter Heideheuvel approved the study.

Study design

The study was performed in a randomised placebo-controlled, double-blind, parallel group design, comparing the effect of allergen-impermeable encasings on the mattresses, pillows and comforts during one year with matching placebo encasings.
At the start of the study a trained respiratory nurse visited the patients in order to collect dust samples from the mattresses of the patients for Der p1 measurement and to notice the allergen avoidance measures already present in the house. All patients included in the study had smooth bedroom floors. Patients were instructed to wash their sheets each week at 60°C. Apart from the mattress encasings no other allergen avoidance measures were taken. At the end of the study the same nurse visited the houses again to collect dust from the mattress encasings.
The patients were included during the entire year; the inclusion period was 2 years. Pollen allergic patients were tested outside the pollen season.
At the first visit patients underwent clinical evaluation. FEV_1 and VC values were measured, skin tests performed and a PC_{20} histamine was assessed. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate one week before the bronchial histamine provocation test, theophyllines, oral ß $_2$- adrenergics, long-acting inhaled ß $_2$-adrenergics and antihistamines 48 hours before the tests and inhaled ß $_2$-adrenergics six hours before the tests.

Collection and extraction of house dust

Collection of dust

Before, at 4 and 8 months and at the end of the intervention, mattress dust was collected by the same vacuum cleaning (Philips type Vitall 377, 1300 watt, Philips, Eindhoven, The Netherlands) of the whole mattress during 2 minutes with a special filter device (ALK, Horsholm, Denmark). At the start of the study dust was collected directly from the mattresses; at the end of the study dust was collected on top of the encasings**.** The filters were stored in the freezer (-20°C) until analysis at the end of the study.

Der p1 Analysis
Der p1 antigen was measured using enzyme-linked immunosorbent assay (ELISA). Monoclonal antibodies against Der p1 were immobilised on a 96-well plate. The incubation with the dust extracts was followed by a second incubation step with a polyclonal antibody (HRP: horseradish-peroxidase). After adding 1,2 phenyldiamine HCL (OPD) as substrate the absorption at 490 nm was measured using an ELISA reader.

Histamine challenge
Histamine phosphate solutions (doubling concentrations from 0.25 to 32 mg/ml) were administered through a De Vilbiss 646 nebulizer with a gauged output of 0.13 mg/ml. The nebulizer was mounted to a valvebox with aerosol filter. The nebulation time was 30 seconds, during which the patient was instructed to breath quietly. The test was started with inhalation of a phosphate buffer aerosol. Prior to the inhalation three measurements of VC and FEV_1 were performed (Jaeger Masterscreen). FEV_1 was measured after each concentration. The PC_{20} histamine was derived by linear interpolation.

Mattress encasings
In the treated group, mattresses, pillows and bedding were encased with covers supplied by Cara C'air (Allergy Control AC btm Velserbroek, Netherlands). The same company made the matched placebo covers. The encasings were placed in position by a research nurse and left in situ during 1 year.

Quality of life
Quality of life was assessed by the Quality of Life for Repiratory Illness Questionnaire (QoL-RIQ) [17]. The QoL-RIQ is a disease specific quality of life questionnaire for patients with asthma and COPD. The questionnaire consists of 55 items divided in seven domains: breathing problems (9 items), physical problems (9 items), emotions (9 items), situations triggering/enhancing breathing problems (7 items), general activities (4 items), daily and domestic activities (10 items), social activities, relationships and sexuality (7 items). To focus the questions to the patient's experiences, items are formulated in terms of 'how much trouble' they had experienced from the mentioned symptom or emotion. In case of activity-like items, questions are stated in terms of 'how much they were impeded' by their disorder in carrying out that specific activity. Patients are asked to give their answer on a 70 point Likert scale ranging from 'not at all' to 'extremely' troubled or impeded. Reliability (test-retest, internal consistency) and validity have been proven. [17].

Clinical parameters
During 14 days before the intervention and at the end of the twelve month intervention the patients were asked to keep diary cards, in which asthma and nasal symptoms, peak flow values and medication use were recorded twice daily. Asthma symptoms included dyspnea, cough, expectoration and wheezing. Nasal symptoms included nasal blockage, rhinorhoea, sneezing and itching. Each item was scored on a scale from 0 (no symptoms) to 4 (severe symptoms). The patients were trained in performing peak flow manoeuvres with the mini-Wright. They were

instructed to perform three readings and to record the highest value, in the morning at awakening and in the evening, before sleeping.
Patients were asked to continue their normal inhalation medication and to record extra rescue medication in case they needed it.

Data analysis
Statistical analyses were performed with SPSS. Comparisons within groups (before and after intervention) were made with the Wilcoxon signed rank test (WSR). Logarithmic data were analysed with the sign test. Mann Whitney U test was used for between group comparisons. P values less than 0.05 were considered significant. Values are expressed as mean value +/- standard error of the mean (SEM) or as median values and range.

Results
Thirty-eight atopic non smoking patients with asthma and house dust mite allergy entered the study. Eight patients did not finish the study, 5 from the placebo group and 3 from the treated group. In the placebo group 3 dropped out because of asthma instability, one because of moving to an other city and because the recording of symptoms, peak flow and rescue medication was not sufficient to make an accurate analysis. In the treated group one individual dropped out because the study was too much of a burden, and two because of insufficient diary keeping. Drop out due to disease instability was significantly higher in the placebo group. 30 patients completed the entire study, 16 patients in the treated group, 14 in the placebo group. The clinical data are presented in Table 1. Although both groups had severe hyperresponsiveness (geometric mean values of PC_{20} histamine 1.75 and 1.27 mg/ml in the placebo and treated group respectively) 3 patients in each group did not regularly use inhaled steroids. Demographic characteristics were similar between the two treatment groups (table 1)**.** There were no significant differences between the two groups regarding to PC_{20} histamine, FEV_1, peak flow values, and medication used.

Der p1 concentrations on mattresses
Figure 1 shows mean log Der p1 concentrations on the mattresses before and 12 months after the start of the study in both groups. In the treated group Der p1 concentrations on the mattresses were significantly lower after 1 year (26.19 $\pm$ 8.58 and 2.79 $\pm$ 0.88 microgram Der p1/g fine dust after 1 year; p=0.004). In the placebo group, there was no significant reduction in Der p1 (23.28 $\pm$ 10.44; 25.11 $\pm$ 11.98 microgram Der p1/g fine dust; p=0.18). There was a significant difference in the treatment-induced change in Der p1 concentration between the two groups (p=0.04). The significant reduction in Der p1 concentration was present after 4 months and persisted throughout the year.

Table 1: Clinical data of the patients

patient	age	sex	FEV_1 (% pred.)	PC_{20} hist (mg/ml)	skin test (*)	rhinitis	medication asthma	medication rhinitis
placebo								
1	21	M	97	1.76	2.1	-	B, SB	-
2	11	M	79	0.74	1.1	+	B, SB	-
3	11	M	97	4.00	1.4	+	B, SB	-
4	29	M	81	0.33	1.2	-	F, SM	-
5	21	M	73	2.43	2.0	+	B, SB	B
6	27	F	70	0.90	1.2	+	B, SB	B
7	44	M	70	1.89	1.2	+	F, SM	F
8	17	F	138	1.78	1.9	+	-	B
9	40	M	64	1.13	1.6	+	B, SB	-
10	29	M	103	0.71	1.5	+	-	-
11	28	F	73	0.45	2.2	-	F, SB	-
12	12	M	106	4.00	1.6	+	B, SB	-
13	25	F	98	1.53	1.5	+	SB	-
14	30	M	100	2.90	1.5	-	B, SB	-
mean	25		89	1.75	1.6			
active								
1	25	F	99	1.19	1.5	+	B,SB	-
2	29	M	99	0.95	1.6	-	B	-
3	41	M	67	3.79	2.2	+	B, SB	-
4	24	F	86	2.00	1.8	+	B, SB	-
5	31	M	81	1.22	1.5	-	-	-
6	24	M	80	0.55	1.1	+	B, SB	B
7	22	F	104	2.67	1.4	+	B	-
8	51	F	70	0.45	1.2	+	B, SB	B
9	32	M	68	0.42	1.1	-	B, SM	-
10	36	F	103	0.35	1.8	+	SB	B
11	42	M	75	0.42	1.2	-	B, SM	-
12	18	F	103	2.35	1.2	+	F, SM	F
13	40	F	98	0.86	1.6	+	B, SB	B
14	30	F	107	1.16	1.9	+	F, SB	F
15	41	F	97	0.98	1.1	-	B, SM	-
16	37	M	76	0.91	1.3	-	SB	-
mean	33		88	1.27	1.5			

*(*) = X times histamine reaction*

B beclomethasone or budesonide; F fluticasone: SB salbutamol

SM salmeterol; FO formeterol

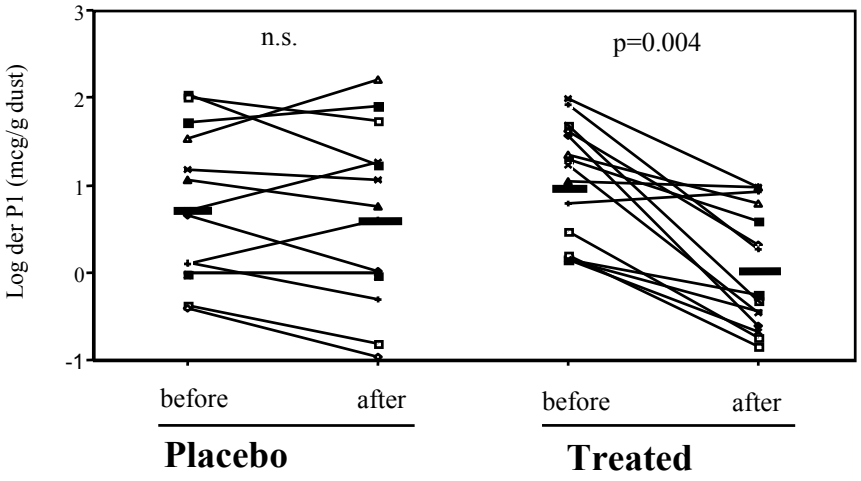

Figure 1: Der p1 before and after 1 year of intervention: log data of mean value of the groups are represented (treated: respectively 0.97 and 0.03. placebo: respectively 0.73 and 0.61 µg Der p1/g dust).

Histamine challenge

At the start of the study mean PC_{20} histamine was 1.45 $\pm$ 0.44 mg/ml and after 1 year 1.66 $\pm$ 0.35 mg/ml in the treated group, the difference being not significant (p=0.64). In the placebo group, there was no significant change in mean PC_{20} over 1 year (before 1.75 $\pm$ 0.32 mg/ml; after 1 year 1.57 $\pm$ 0.28 mg/ml: p=0.97). Treatment-induced changes in PC_{20} histamine were not significantly different between the two groups (p=0.77).

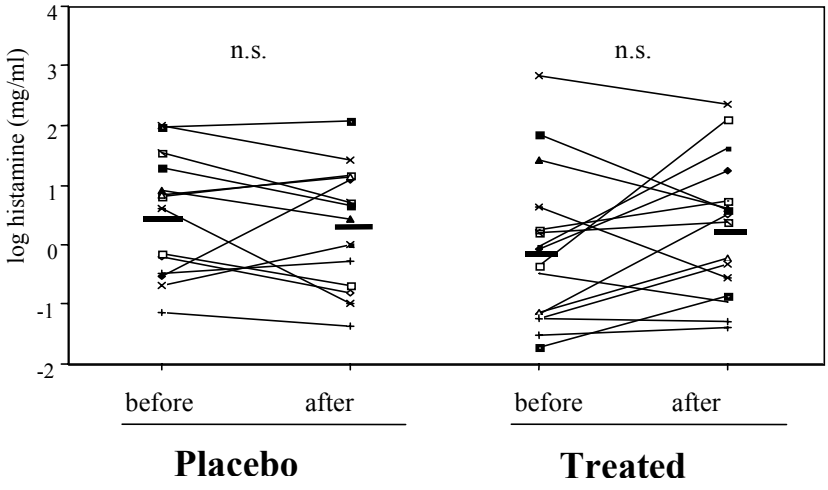

Figure 2 : PC_{20} histamine before and after 1 year of intervention: logarithmic values are presented. The geometric mean value of the groups are represented by lines (-) (active: respectively –0.11 and 0.28. placebo: respectively 0.48 and 0.33 mg/ml.)

TABLE 2: SYMPTOM SCORES BEFORE AND AFTER INTERVENTION

PULMONARY SYMPTOMS					
placebo group			**treated group**		
patient	before	after	patient	before	after
1	1.50	0.21	1	2.71	0.42
2	1.33	5.20	2	0.64	3.00
3	1.07	3.14	3	3.30	5.85
4	0.92	0.00	4	2.14	1.30
5	2.38	4.78	5	0.07	0.00
6	6.38	0.43	6	2.00	1.64
7	2.00	0.28	7	1.14	1.50
8	8.35	10.92	8	8.25	7.07
9	0.14	0.21	9	3.14	2.78
10	0.21	0.21	10	0.92	0.35
11	1.21	0.14	11	0.00	1.25
12	4.33	3.50	12	2.42	5.28
13	0.75	4.14	13	4.00	4.09
14	0.00	0.00	14	2.07	1.42
			15	0.00	0.00
			16	0.00	0.00
median	1.27	0.36		2.04	1.46
range	(00-8.35)	(00-10.92)		(00-8.25)	(00-7.07)

NASAL SYMPTOMS					
placebo group			**treated group**		
patient	before	after	patient	before	after
1	1.71	0.86	1	4.57	2.42
2	2.14	4.00	2	3.21	2.16
3	2.50	5.70	3	2.30	4.28
4	0.00	0.00	4	2.50	0.10
5	5.00	2.50	5	1.42	0.57
6	5.23	4.71	6	0.64	0.50
7	1.00	0.00	7	6.57	5.21
8	7.64	10.92	8	5.00	4.07
9	0.35	0.71	9	1.92	2.00
10	0.64	0.28	10	3.23	0.50
11	0.14	0.00	11	0.00	0.00
12	11.16	2.00	12	1.42	1.00
13	2.85	2.71	13	0.16	1.00
14	0.00	0.00	14	0.75	0.42
			15	0.00	0.00
			16	0.00	0.00
median	1.93	1.43		1.67	0.79*
range	(00-11.16)	(00-10.92)		(00-6.57)	(00-5.21)

mean values of 14 days of registration

** in treated group significant difference after 1 year compared to before (p=0.04)*

TABLE 3: PEAK FLOW VALUES BEFORE AND AFTER INTERVENTION

MORNING PEAK FLOW						
placebo group				**treated group**		
patient	before	after		patient	before	after
1	581	549		1	365	409
2	315	240		2	727	740
3	395	342		3	416	450
4	nd	nd		4	312	337
5	467	550		5	619	588
6	292	336		6	517	501
7	536	554		7	437	455
8	520	512		8	319	328
9	432	416		9	460	437
10	475	600		10	329	365
11	370	354		11	398	340
12	375	347		12	500	480
13	400	380		13	226	246
14	548	542		14	368	388
				15	476	446
				16	450	444
median	432	416			426	440
range	(292-581)	(240-600)			(226-727)	(246-740)

EVENING PEAK FLOW						
placebo group				**treated group**		
patient	before	after		patient	before	after
1	563	553		1	396	406
2	288	236		2	683	748
3	434	343		3	516	470
4	nd	nd		4	346	390
5	509	565		5	634	601
6	289	326		6	502	506
7	534	592		7	444	456
8	529	516		8	380	374
9	431	406		9	399	411
10	625	700		10	370	386
11	351	362		11	400	351
12	375	346		12	497	484
13	380	400		13	225	247
14	556	552		14	362	360
				15	570	485
				16	449	440
median	434	406			422	425
range	(228-625)	(236-700)			(225-683)	(247-748)

mean values of 14 days of registration
no significant differences between the groups

Table 4: Overview of results and setup of controlled mattress cover studies

author	**study set up**						**parameters**				
	N	age	design	duration (wk)	carpet	acaricide	Der p1	PC_{20} hist	symptoms	peakflow	medication
Sarsfield 1974	14	children	open c	52	-	-	+	nd	+	nd	nd
Murray 1983	20	children	pl c	4	-	-	-	+	+	nd	nd
Walshaw 1986	50	adults	pl c	52	+	-	+	+	+	nd	nd
Gillies 1987	24	children	open c	12	+	-	-	-	-	nd	nd
Ehnert 1992	24	children	open c	52	+	+	+	+	nd	nd	nd
Marks 1994	35	adults	r c	26	+	+	-	-	-	-	nd
Weeks 1995	56	children	r db pl	24	+	+	+	nd	nd	nd	nd
Carswell 1996	70	children	r db pl	24	+	+	+	-	nd	-	nd
vd Heide 1997	59	adults	open c	52	+	+	+	+	nd	nd	nd
Frederick 1997	31	children	r sb pl	12	+	-	+	-	-	-	-
vd Heide 1997	45	adults	open c	26	+	-	+	-	nd	nd	nd
Cloosterman 1997	29	adults	r sb pl	6	+	+	nd	nd	+	-	nd
Sporik 1998	85	children	open c	78	+	+	-	nd	nd	nd	nd
Cloosterman1999	157	adults	r db pl	20	+	+	+	-	-	-	nd

open c: open controlled
pl c: placebo controlled
r c: randomized controlled
r db pl: randomized double blind placebo controlled
r sb pl: randomized single blind placebo controlled

nd: not done
+ significant change
- not significant change

Quality of life

Overall QoL scores were comparable at baseline in the placebo and in the treated group. The same was true for the subdomains. Clinical relevant improvements (difference >0.5) [18] were seen in the domains breathing problems, physical problems related to chest problems, triggering/enhancing circumstances and total score both in the treated and in the placebo group. Although the size of the improvements did not significantly differ between the two groups, improvements within the treated group were significant.

Clinical parameters

Baseline values of asthma symptom scores showed no significant differences between the groups (table 2). Median pulmonary symptom score did not significantly change over one year in both groups. There was a significant decrease in the nasal symptom score in the treated group (p= 0.04), but not in the placebo group; the difference between the two groups was not significant. Baseline peak flow values (morning and evening) were comparable for both groups (table 3). One year of intervention did not result in significant changes in the morning or the evening peak flow values, nor in the peak flow variability, and the use of rescue medication in both groups.

Discussion

This study was performed in order to investigate the effect of anti-allergic mattress encasings in carpet free bedrooms on Der p1 exposure in the bed and on clinical parameters in patients with moderate to severe asthma with house dust mite allergy. We found a significant reduction in Der p1 concentration in the dust collected from the mattresses in the actively treated group compared to the placebo group. PC_{20} histamine did not improve over 1 year of treatment. Although there was a significant improvement in nasal symptoms and quality of life observed only in the actively treated group, we found no significant difference between the placebo and active group in the change of pulmonary and nasal symptoms, quality of life, peak flow values and rescue medication.

Earlier studies using several different types of mattress encasings have also shown a reduction of Der p1 exposure on top of the mattress (table 4) [8-10;19;20]. However other studies did not show a reduction in Der p1 concentrations and remarkably the carpets in the bedroom were not removed in these studies in particular [21;22]. We excluded the problem of Der p1 contamination from the floor [13] by including only patients in this study who had uncarpeted floors in their bedroom. This may have contributed to the fact that we could reach a significant reduction in the actively treated group even though we had rather high baseline Der p1 concentrations compared to other studies [22;23]. The reduction in allergen concentration was reached after 4 months, and remained during the whole study period.

Although Der p 1 concentrations were significantly reduced in the active group compared to the placebo group, we did not find a significant reduction in bronchial hyperresponsiveness.
Other studies also failed to demonstrate an improvement in bronchial hyperresponsiveness [10;11;22]. Two studies [22;23] did not find a substantial reduction in allergen concentrations in dust which explains the lack of improvement in bronchial hyperresponsiveness. Frederick[10] et al stated

that all patients were reasonably controlled on regular prophylactic therapy. Therefore little or no change in clinical parameters could be expected. But even Cloosterman and co-workers [11], who tried to avoid this treatment effect by including only patients who either did not use inhaled steroids or were able to stop them, did not find a significant improvement in bronchial hyperresponsiveness, nor in any of the clinical parameters used like symptom score, peak flow variability and reversibility of FEV_1. How can we reconcile these observations? Patients participating in our study had severe hyperresponsiveness, despite relatively high doses of inhaled corticosteroids ($\geq$800 microgram) (for comparison PC_{20}< 4 microgram/ml with 30' method is comparable to 1mg/ml in the 2 minutes method). Thus, despite suppression of airway inflammation by use of inhaled steroids for years, severe hyperresponsiveness remained. Airway inflammation and bronchial hyperresponsiveness are induced by repeated inhalation of low doses of allergen [24]. However one year of reduction in house dust mite-exposure might be a too short period as one concerns the life time exposure most patients have had before the intervention. One can hypothesise that the persistence of severe hyperresponsiveness is related to airway remodelling, the structural changes in bronchial architecture as a result of chronic airways inflammation [25]. Hence no further improvement can be expected with allergen reduction that most likely affects acute inflammation, in this stage of already established disease.

Until now there are no data on the effect of avoidance measures on Quality of Life. Clinical relevant improvements in Quality of Life were found in both groups. The instrument we used is a questionnaire specific for asthma and COPD. Our study focused on the allergic component of asthma, which was represented by only three of the 55 items. This may partially explain the lack of difference between the two groups. Alternatively, allergen reduction may not affect the outcome of QoL and the improvement in both the intervention and placebo group may reflect rather the special attention the patient received during the study period. The important question in allergen avoidance studies is whether the used avoidance technique improves asthma control in sensitised patients.[1] There are a few double blind placebo controlled studies (table 4) which assessed allergen avoidance measures relating to symptoms. When reviewing these studies it is clear that improvement in symptoms was noticed in 4 studies [14;24;26;27]. Two of them studied children [26;27], one studied patients with mild asthma and one studied allergic patients who had not developed asthma yet (subclinical). Other studies [11;22], even in children [10;23] did not find a reduction in symptoms as we found in our study. The peak flow was recorded in 7 studies, 2 found a significant increase in patients with mild and preclinical asthma [14;28], where as 5 no significant increase [10;12;19;22;23]. Medication was recorded in one study without a positive result [10]. Taken together, the data suggest that the contribution of allergen avoidance measures is ineffective in patients with moderate to severe asthma. The severity of the clinical manifestation is influenced by more factors such as other allergens, viruses and air pollution, which are not influenced by the avoidance measures. Surprisingly there are no controlled data of allergen avoidance on nasal symptoms in literature. In our study rhinitis symptoms were scored in addition to asthma symptoms. We found a significant improvement in nasal symptoms in the treated group, although the difference between the two groups was not significant the nose seems to be more responsive to avoidance measures than the lower airways. Therefore it might be interesting to do

avoidance studies in rhinitis patients in a controlled way using subjective and objective parameters.

Summarising our data, we show that the use of anti-allergic mattress encasings results in reduction of Der p1 concentrations in carpet-free bedrooms. In patients with moderate to severe asthma airways hyperresponsiveness and clinical parameters do not change. Because lack of effect may be due to the chronic stage of the asthma and/or avoidance measures limited to the bedroom further studies have to explore whether night-time and daytime avoidance measures in early stage of disease is more effective.

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Chapter 6

Comparison of a generic and a skin disease specific quality of life instrument in patients with atopic dermatitis: Factor analysis of the Questionnaire on Coping with Skin Disease (QCSD) and relationship with the SF-36.

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Submitted

Comparison of a generic and a skin disease specific quality of life instrument in patients with atopic dermatitis: Factor analysis of the Questionnaire on Coping with Skin Disease (QCSD) and relationship with the SF-36.

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Summary

Background: Quality of life (QoL) instruments the SF-36 and Questionnaire of coping with skin diseases (QCSD) are instruments aimed to monitor not only the progress but also the state of health-related QoL issues of patients with chronic skin diseases like atopic dermatitis (AD).

Objective: To analyse the empirical structure of the disease specific QCSD translated into Dutch- and to study the relationship with the generic SF-36. Secondly, to evaluate the impact of AD on QoL.

Methods: AD patients (18-50 years) who were allergic to house dust mite (HDM) and did have a Leicester Sign Score (LSS, a dermatitis score) of at least 1 % extent and a severity score of 6 points filled in the QCSD and the SF-36 questionnaire. The empirical structure of QCSD was identified with the methods of factor analysis, the interrelationship of QCSD and SF-36 was estimated by canonical correlation.

Results: Factor analysis with QCSD yielded two principal factors, labelled as 'Feeling hurt' and 'Emotional distress', respectively. Canonical correlation of the QCSD and the SF-36 yielded one significant canonical variate. 'Emotional distress' loaded completely 1,0 on this variate together with the SF-36 factors vitality (VT) and mental health (MH) which loaded -0.88 and -0.86 respectively. The percentage of redundancy for the QCSD and the SF-36 subscales were 40 and 30, respectively. Comparison of the SF-36 data of the AD study population with the general Dutch population showed an impairment of the factors general health (GH), vitality (VT) in patients with AD.

Conclusions:The QCSD can be condensed from a 42 items to a 16 items questionnaire comprising two principal factors called 'Feeling hurt' and 'Emotional distress'. Although disease specific QCSD and generic SF-36 have a discernible overlap, both questionnaires have substantial unique qualities. Comparison with other study populations demonstrated that patients with active AD are impaired.

Abbreviations

AA: Allergic asthma
AD: Atopic dermatitis
AR: Allergic rhinitis
BP: Bodily pain
CDLQI: Children's dermatology life quality index
DLQI: Dermatology life quality index
EADV: European academy of dermatology and venereology
GH: General health
HDM: House dust mite
LSS: Leicester sign score
MH: Mental health
PF: Physical functioning
QCSD: Questionnaire of coping with skin diseases
QoL: Quality of life
RE: Role emotional functioning
RP: Role physical functioning
SF: Social functioning
SMC: Squared multiple correlations
VT: Vitality

Introduction

Quality of life (QoL) instruments are becoming important in the evaluation of therapy. They can be distinguished by disease-specific and generic instruments. Disease specific instruments are believed to be more sensitive for changes due to intervention within a diagnostic group, while generic are predominantly tailored to general well being.[1]

Chronic skin diseases impair QoL as has been assessed with different QoL questionnaires. The importance of QoL in treatment of skin diseases has been underscribed by the European Academy of Dermatology and Venereology (EADV), they proposed the following recommendations: dermatologists should incorporate health-related quality of life measurements to help assess and monitor the progress of their patients; research is required to develop and refine such health-related quality of life instruments and therapy should clearly demonstrate a positive influence on health-related quality of life.[2;3] The British association of dermatologists already tried to properly implement and evaluate these guidelines.[4]

Several questionnaires were developed and used in clinical trials. The German Questionnaire of Coping with Skin Disease (QCSD), a 42-items self-administered survey instrument intended for AD only, with 5 scales: social stigmatisation, restrained emotional coping with the disease, general emotional distress, awareness of restriction in active, problem-related coping, impact on QoL.[5] A variant of this questionnaire with 51 items was used in other studies.[6;7] The most well-known questionnaire has been the Dermatology Life Quality Index (DLQI) having developed by Finlay and Kahn 1994 which was intended as a compact self-administered questionnaire suitable for patients with any skin disease (acne, psoriasis, AD).[8] It comprises six factors of ten items altogether dealing with: 1 symptoms and feelings, 2 daily activities, 3 leisure, 4 work and school, 5 personal relationships and 6 treatment. Also a children's variant, i.e. the CDLQI was developed.[9;10]

One of the most widely used generic quality of life instruments is the SF-36 having been developed from the Rand Corporation's Health Insurance Experiment in the USA in 1992. The SF-36 measures health-related quality of life comprises eight factors. These eight factors are: 1 physical functioning(PF): limitations in physical activities because of health problems; 2 role-physical functioning(RP): dealing with limitations in usual role activities because of physical health problems; 3 bodily pain (BP); 4 general health perceptions (GH); 5 vitality (VT): indicating lack of energy and fatigue; 6 social functioning(SF): with regards to limitations in social activities because of physical or emotional problems; 7 role-emotional functioning(RE): on limitations in usual role activities due to emotional health problems; and 8 mental health (MH).[1;11;12]

AD is a visible disease; patients get symptoms of erythema, scaling, lichenification amongst others, which can not be easily hidden. One can imagine that this could induce feelings of impairment emanating to frustration and even depression, which can be measured by QoL instruments. A study performed by a Swedish group[2] did show impairment of QoL as measured with the SF-36 and DLQI.

The objective of this project was to analyse the empirical structure of the translated QCSD and to identify the emperical overlap between the QCSD and the SF-36.

Material and methods

Patients

The sample consisted of adults(18-50 years). All patients were allergic to house dust mite as measured with the skin prick test (10.000 Bu/ml, ALK-ABELLO, Spain). AD patients with or without allergic asthma (AA) or allergic rhinitis (AR) were permitted to the study, if the met the criteria of Hanifin and Rajka.[13] In addition, to ensure that patients did have active atopic dermatitis a score system was used. We used the Leicester sign score (LSS) for AD distinguished by severity and extent scores, respectively.[14] Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification) generated a total body disease activity score, the LSS severity score (with minimum 0 and maximum 108). Extent of the disease was assessed according to the "rule of nines" and resulted in the LSS extent score (with minimum 0 and maximum 100 %). Also a composite score was created called LSS composite by multiplying LSS severity with LSS extent. A LSS of at least 1% extent and 6 points severity was required.

Assessments

QoL was measured using an AD specific questionnaire, the QCSD. The QCSD was translated from German to Dutch. It is a 42-items self-administered survey instrument intended for AD with 5 scales: social stigmatisation, restrained emotional coping with the disease, general emotional distress, awareness of restriction in active, problem-related coping, impact on QoL.[5] A high score, range 1-5, indicates a low QoL whereas a low score indicate a good QoL.

QoL was also measured with a generic questionnaire, the SF-36, We used the translation of Aaronson of the MOS SF-36, originally developed by Ware and co-workers.[1;12;15-17] SF-36 consists of 36 questions covering eight subscales, representing both a physical and a mental health summary component. Physical health subscales are physical functioning (PF), role physical functioning (RP), bodily pain (BP) and general health (GH); mental health subscales are mental health (MH), role mental functioning (RE), social functioning (SF) and vitality (VT). Questions are stated in both yes/no form and multiple choice. Sum score is calculated for each subscale and transformed to a percentage of the total possible score. The physical health component consists of PF, RP, BP, GH and the mental health component consists of MH, RE, SF and VT. High score indicates good QoL, whereas low score indicates low quality of life. The reliability in two general populations samples as reported by Aaronson using Cronbach's alpha varied from 0.76 to 0.92 while the item discriminant validity varied from 0.09 to 0.64.

Study design
Patients were recruited from a multicenter trial which studied the effect of encasings of mattresses, pillows and duvets on complaints of allergic rhinitis and/or asthma and/or AD and from the AD population which visited the outpatient clinic Dermatology in Utrecht and Rotterdam in the period 1996-2000. Participating centres were the Allergology departments of the University Hospitals of Groningen and Rotterdam and the Dermatology department of the University Hospital Utrecht. The Medical Ethics Committees of all three University Hospitals approved the study and all patients gave written informed consent. Patients visited the clinic for baseline measurements on two consecutive days for tests. As part of this study they filled in generic and disease-specific questionnaires.

Procedures
The generic SF-36 questionnaire was administered before the disease-specific QCSD questionnaires. Trained personnel instructed the patient according to the guidelines, defined by the designers of the questionnaires. To ensure privacy and a quiet environment patients could fill in the questionnaires in a pravate roomwithout the presence of other persons.

Statistical analysis

Factor analyses
As we used a non-validated translation of the QCSD factor analysis was performed to identify the underlying empirical structure. Actually, the factor analysis attempts to represent the items in small number of factors (factors, latent variables) without substantial loss of information. In this study the principal factoring method was applied. The number of factors extracted was determined by two criteria: 1. the percentage of variance explained by the factors extracted and 2. the interpretability of the solution after orthogonal (VARIMAX-) rotation. The importance of the items was derived from the loadings (correlations) of the items on (with) the rotated factors: theoretical maximum equals 1,00 whereas the minimum equals –1,00. Factors were characterised by high loadings, positively or negatively, and loadings as close as 0.00 as possible on the remaining factors. Labelling of the factors rotated was predominantly based on the items with the high(est) loadings, positively and negatively. Also the reliability was calculated which measures to what extent an item, scale or instrument yields the same score in different scales, populations or times. The Pearson correlation was performed to analyse the correlation between the factors of the QCSD and the activity of AD as measures with the LSS score. The analyses were performed with the SPSS 9.0 package.

Canonical correlation
The interdependency of the QCSD subscales and the SF-36 subscales was analysed with the method of canonical correlations for continuous data.[18-20]Actually, canonical correlation studies the interrelationship of two sets, i.e. atopic dermatitis and general quality of life subscales respectively, in terms of the number and nature of factors of correspondence. Actually, only the first two or three factors are reliable and can really be interpreted.

A relevant condition of proper use of canonical correlation is that the variables have multivariately a normal distribution. In this study the distribution was a bit skewed, but log-transformation yielded almost identical results. Therefore, the analyses were performed on untransformed variables.
Linearity is assumed in canonical analysis. To investigate whether the interrelationships were linear, the multivariate normality and homoscedasticity, pairs of canonical variates were plotted against each other. Finally, it is of relevance that the variables within and across each set are not too highly intercorrelated. Squared multiple correlations (SMC) as a measure to identify multicollinearity and singularity were performed. It appeared that SMCs did not become very large (range: 0.29 - 0.59). The conclusion is justified that there is discernible heterogeneity in the two sets of variables. BMDP Statistical Software was used for all analyses.

Results

General results
In all, 109 eligible patients with atopic dermatitis were included in the study. In Table 1 the general characteristics of the included population are presented.

Table 1: General characteristics of the study population (N=109)

		%
Gender (m/f)	46/63	42.2%:57.8%
Age (mean, standard deviation(s.d.))	29.8 ± 8.6	
LSS Severity (median, range)	19 (6-70)	
LSS Extent (median, range)	26 (2-99)	
LSS Composite (median, range)	506 (14-5544)	
Somatic Comorbidity	Frequency	
AE	19	17.4%
AE + AR	29	26.6%
AE + AA	7	6.4%
AE +AR + AA	54	49.5%

Factor analysis
Factors were extracted from the QCSD items. In Table 2 the factor loadings of the items of the QCSD are presented. Factor loadings of more than 0.55 on one factor and less than 0.40 on other factors were considered to be of importance Two factors remained and were called ‘Feeling hurt’ and ‘Emotional distress’, respectively. The reliability of the items of the factors was 0.93 and 0.89 respectively.

Table 2: Empirical structure determination of the QCSD

No.	Questions	Factor I Feeling hurt	Factor II Emotional distress
20	I have the feeling that someone looks at my skin	0.69	0.30
36	I sometimes think how it would be to live without this skin condition	0.67	0.11
12	It bothers me that other people can see my scratched skin	0.66	0.17
2	Due to my skin disease I feel less attractive compared to other people	0.65	0.36
40	I am angry at myself when I undo the laborious reached results by scratching	0.64	0.19
39	Itching makes me desperate	0.64	0.23
15	It takes me a lot of energy to refrain from scratching	0.62	0.10
29	It frightens me that my skin disease will worsen	0.61	0.12
17	I won't go to a sauna or swimming pool due to being ashamed of my skin disease	0.61	0.29
		Factor I Feeling hurt	Factor II Emotional distress
19	I feel often tired	0.15	0.80
25	I am lacking of energy often	0.13	0.75
13	I am faster overburdened compared to others	0.24	0.69
5	I feel often nervous	0.25	0.68
10	I worry about small matters	0.19	0.66
38	A lot of things I am taking personally	0.06	0.65
41	I should burden myself with less stress	0.13	0.58

*) Factor loadings are presented

Impact of AD on QoL

Table three shows the Pearson poroduct-moment correlation of the QCSD factors with the LSS scores. Significant correlations exist between the QCSD factor 'Feeling hurt' and the LSS scores severity, extent and composite. The QCSD factor 'Emotional distress' correlated significantly with the LSS scores extent and composite. Table four presents the univariate statistics of the QoL factors of the QCSD and SF-36. The outcome of the SF-36 was compared with the results obtained from the general Dutch population. As data from another Dutch AD population were not available, a Swedish AD population was chosen for comparison.

Table 3: Pearson correlation between the QCSD factors “Feeling hurt”; “Emotional distress” and LSS severity, extent and composite score (N=109).

	Feeling hurt	Emotional distress
LSS severity	0.40**	0.19
LSS extent	0.26**	0.21*
LSS composite	0.34**	0.22*

* $p<0.05$
** $p<0.01$

Table 4: Univariate statistics of QCSD and SF-36 subscales in different populations.

Subscales (range)	Dutch AD population n=109 (mean, s.d.)	Dutch general population n=1742 (mean, s.d.)[1]	Swedish AD population n=132 (mean, s.d.)[2]
QCSD (1-5)			
Feeling hurt	2.8 ± 0.7	N/A.	N/A.
Emotional distress	2.2 ± 0.7	N/A.	N/A.
SF-36 (0-100)			
PF	86.7 ± 15.0	83.0 ± 22.8	85.1 ± 19.0
RP	79.1 ± 30.9	76.4 ± 36.3	66.7 ± 39.2
GH	64.2 ± 21.1	70.7 ± 20.7	62.1 ± 24.2
BP	78.8 ± 20.9	74.9 ± 23.4	66.2 ± 29.9
SF	82.0 ± 20.7	84.0 ± 22.4	81.0 ± 23.5
VT	62.5 ± 19.7	68.6 ± 19.3	57.0 ± 21.6
MH	77.2 ± 14.5	76.8 ± 17.4	73.2 ± 19.0
RE	84.4 ± 31.9	82.3 ± 32.9	74.0 ± 37.4

N/A=Not available

Interrelationships of QCSD and SF-36

The intra- and inter-relationship of the QCSD subscales and the SF-36 subscales (see Table 5) were estimated by the Pearson product-moment correlation. The intrarelationship of ‘Feeling hurt’ with ‘Emotional distress’ was 0.54; the intrarelationship of the SF-36 subscales was located between 0.12 and 0.67. The interrelationship of the QCSD subscales and the SF-36 subscales varied from -0.71 to -0.03, The matrix of intra- and intercorrelation were analysed on behalf of the method of canonical correlation

Table 5: Intercorrelation of the QCSD and the SF-36 subscales

	Feeling hurt	Emotional distress		PF	RP	GH	BP	SF	VT	MH	RE
Feeling hurt	1.00										
Emotional distress	0.54	1.00									
PF	-0.03	-0.24		1.00							
RP	-0.14	-0.49		0.58	1.00						
GH	-0.23	-0.52		0.58	0.49	1.00					
BP	-0.18	-0.45		0.43	0.42	0.53	1.00				
SF	-0.25	-0.53		0.14	0.48	0.21	0.16	1.00			
VT	-0.30	-0.71		0.32	0.55	0.51	0.44	0.39	1.00		
MH	-0.37	-0.70		0.12	0.35	0.36	0.36	0.62	0.67	1.00	
RE	-0.25	-0.53		0.14	0.48	0.21	0.16	1.00	0.39	0.62	1.00

Table 6 shows the results of the significance testing. Bartlett's test was used to extract the number of canonical variates required to adequately express the relationship between the QCSD and SF-36.

Table 6: Significance testing of the canonical correlation between QCSD and SF-36

Eigenvalue	Canonical correlation	Number of eigenvalues	Chi-square	df	p
			114.56	14	0.00
0.66	0.81	1	2.59	6	0.86
0.02	0.16				

In the canonical correlation analysis pairs are extracted until it either runs out of variables on one set or until no more significant relationships are identified. The number of pairs or variates is the number of factors along which the sets of variables are related. Bartlett's test indicated that there was one canonical variate needed to adequately express the interdependency of QCSD subscales and the SF-36 subscales. In other words, the first canonical variate accounts for the significant relationship between the QCSD subscales on the one hand and the SF-36 subscales on the other.
The eigenvalue represents the variance of the canonical variates; the canonical correlation is the square root of the eigenvalue. In this study the correlation in the first pair of canonical variates turned out to be 0.81, which corresponded to explained variance of 0.66 (i.c. eigenvalue).

In Table 7 the analysis of the first canonical variate belonging to the canonical correlation is presented. Of the QCSD subscales the subscale'Emotional distress' correlated completely with the first canonical variate (1,0) and the subscale 'Feeling hurt' correlated less (0.46) although moderate.
The second extracted canonical variate turned out to be non-significant. Of the SF-36 subscales VT (-0.88) and MH (-0.86) loaded negative but very high on the first canonical variate, all other subscales loaded -0.56 to -0.65, with the exception of PF which loaded low (-0.31).

The proportion of variance for each canonical variate extracted from each set of variables (QCSD and SF-36 subscales, respectively), which equals the sum of the loadings squared, divided by the number of variables in the set, is shown in Table 8. The significant first canonical variate of the QCSD subscales extracted 60 percent of the variance. For the SF-36 subscales the first canonical variate extracted 45 percent of the variance. The redundancy analysis which tells how much canonical variates from one set can be extracted from the other set and vice versa is also shown in Table 7. The redundancy is the average square loading multiplied by the canonical correlation, which equals the average squared correlation of a variable in one set with the canonical variate in the other set, meaning the percentage of variance extracted from its own set of variables multiplied by the canonical correlation

squared for the pair. Only the first pair was significantly correlated. The redundancies for the QCSD and SF-36 subscales were 40 percent and 30 percent, respectively.

Table 7: Canonical variate loadings of QCSD and SF-36

Table 7: Canonical variate loadings of QCSD and SF-36	
Factor	I
Set 1: QCSD	
Feeling hurt	0.46
Emotional distress	1.00
Set 2: SF-36	
PF	-0.31
RP	-0.62
GH	-064
BP	-0.56
SF	-0.65
VT	-0.88
MH	-0.86
RE	-0.65

Table 8: Redundancy of QCSD and SF-36 subscales

Canonical variate	Average squared loading for every canonical variate, QCSD	Average squared loading for every canonical variate, SF-36	Average loading squared multiplied by SCC, QCSD	Average loading squared multiplied by SCC, SF-36	Squared canonical correlation (SCC)
I	0.60	0.45	0.40	0.30	0.66

Discussion

From factor analysis two principal factors ‘Feeling hurt’ and ‘Emotional distress’ emerged, comprising 16 items. A couple of limitations have to be addressed. Our results differ from the original construction of the QCSD comprising five factors and 42 items.[21] It is not precluded that in the Dutch patient population the condensed QCD is sufficient to characterise limitations in QoL of patients with atopic dermatitis. Alternatively the relatively low number of AD patients in this study (n=109) compared to the original study (n=209)[21] might have explained the divergent empirical structure.

Comparing the items of ‘Feeling hurt’ and ’Emotional distress’ with the items of the original article with five factors[5] revealed that the 16 items of the two factors of the Dutch QCSD

corresponded with the items of the first three factors of the original article. All items of the factor ‘Feeling hurt’ corresponded to the original two factors: 1) Social stigmatisation: adverse affection of outer appearance, loss of attractivity and fear of social depreciation; and 2) Restrained emotional coping with the disease: experience of being threatened, perceived lack of controllability. All items of ’Emotional distress’ corresponded to the items of the third factor ‘General emotional distress’ representing symptoms of depression and anxiety of the original article.

Disease-specific and generic QoL instruments have been interchangeably used in clinical research. This can only be justified, if both instruments were highly interrelated. Indeed, ‘Increased feeling of fatigue’ and ‘Lack of energy (VT)’ together with ‘Impairment of mental health’ (MH) was highly related with ‘Emotional distress’. In addition, the interdependency between the AD specific questionnaire and the generic SF-36 questionnaire measured with the canonical analyses was substantial but not (too) high. The percentage of redundancy coefficients 0.40 and 0.30 for QCSD and SF-36, respectively. It has to be concluded that the instruments are not interchangeable. One might argue that because comorbidity is present in most AD patients a generic questionnaire is desired next to a disease specific instrument to assess QoL.

It appeared that AD limits QoL in affected patients. As expected the Dutch AD population seem to have impaired QoL compared with the general Dutch population.[1] Patients scored lower on the SF-36 subscales GH, VT.

In conclusion, the QCSD can be condensed from a 42-item to a 16-item questionnaire comprising ‘Feeling hurt’ and ‘Emotional distress’, respectively. Although disease specific QCSD and generic SF-36 display overlap, neither questionnaire can substitute the other.

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Chapter 7

Longitudinal double-blind placebo controlled study of effect of mattress encasings, house dust mite and Atopic Dermatitis on a generic questionnaire, the SF-36

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Submitted

Longitudinal double-blind placebo controlled study of effect of mattress encasings, house dust mite and Atopic Dermatitis on a generic questionnaire, the SF-36

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Summary
Background: Atopic Dermatitis (AD) is a chronic skin disease and occurs often with allergic asthma (AA) and allergic rhinitis (AR). It can have a profound effect on quality of life (QoL). Several studies assessed QoL in AD, but there is no knowledge about how change of clinical (classical) parameters changes QoL parameters.
Objective: To analyze to what extent site and severity of AD influences the SF-36, a generic quality of life (QoL) questionnaire and if it is affected by exposure to HDM, age, gender and treatment with mite-impermeable encasings.
Methods: AD patients (18-50 years) who were allergic to house dust mite (HDM) and did have a Leicester Sign Score (LSS, a dermatitis score) of at least 1 % extent and a severity score of 6 points, were randomly allocated to an active (n=31) or a placebo allergen-avoidance group (n=33). Avoidance measures consisted of applying HDM-impermeable covers for mattresses, pillows, duvets and cotton covers for the placebo group. Effect on the allergen concentrations (Der p1 + Der f1), LSS extent and severity and Quality of Life as measured with the SF-36 were studied. For analysis the physical components summary (PCS) and mental components summary (MCS) were used.
Results: The decrease of Der p1 + Der f1 concentration was not significant in both AD treatment groups after applying the avoidance measures for four and twelve months. Longitudinal analysis showed that the PCS is specified by three covariates: linear time as a positive effect and having AD at the trunk and arms with both a negative effect. The MCS is specified by having AD at arms and trunk, which both have a negative effect.
Conclusions: This study reports for the first time a relation between presence of AD on specific sites of the body and effect on the SF-36. Having AD at the trunk and arms results in an impairment of PCS, probably due to the body area involved. Passing of time results in an improvement of PCS, which could be caused by adaptation to a longer lasting presence of AD. This could be one of the weak spots of QoL measures, patients perceptions may shift in time independent of their disease severity, leading to a different relation between clinical aspects of a disease and quality of life in time. Having AD at trunk or arms results in an impairment of MCS.

Keywords Atopic dermatitis, quality of life, questionnaire, SF-36, Leicester Sign Score, house dust mite, longitudinal analysis, body site specific, double-blind placebo controlled

Abbreviations

AA: Allergic asthma
AD: Atopic dermatitis
AR: Allergic rhinitis
BP: Bodily pain
GH: General health
HDM: House dust mite
LSS: Leicester sign score
MH: Mental health
PF: Physical functioning
QoL: Quality of life
RE: Role emotional functioning
RP: Role physical functioning
SF: Social functioning
SMC: Squared multiple correlations
VT: Vitality

Introduction

Atopic Dermatitis is a chronic skin disease and is part of the atopic syndrome, as such it can occur together with allergic asthma and allergic rhinitis. The prevalence of having a respiratory allergy combined with AD varies from 50-70 %[1-4] which can have a large impact on QoL.[5-7] It might be recommendable to use a generic questionnaire to measure the complete impact of the combined atopic diseases within the AD population. Improvement of AD by beneficial effects of house dust mite avoidance measures like mattress, pillow and duvet[8-11], could lead to improvement of QoL.

In this study the well-known SF-36, a generic quality of life instrument, was used. It was developed in 1992 from the Rand Corporation's Health Insurance Experiment in the USA. The SF-36 measures health–related quality of life comprises eight dimensions. These dimensions are: 1 physical functioning(PF): limitations in physical activities because of health problems; 2 role-physical functioning(RP): dealing with limitations in usual role activities because of physical health problems; 3 bodily pain (BP); 4 general health perceptions (GH); 5 vitality (VT): indicating lack of energy and fatigue; 6 social functioning(SF): with regards to limitations in social activities because of physical or emotional problems; 7 role-emotional functioning(RE): on limitations in usual role activities due to emotional health problems; and 8 mental health (MH).[12-15]

The primary objective of the study is to test to what extent site and severity of AD influences QoL. Longitudinal testing of these effects within the context of a randomized clinical trial can address the question whether generic Qol could be effected not only by disease severity but also by exposure to HDM, age, gender and above all by treatment with mite-impermeable encasings.

Material and methods

Patients

Patients with AD aged between 18 and 50 years were recruited from the dermatology, Allergology and pulmonary outpatient clinic at the University Hospital in Utrecht, Rotterdam and Groningen (the Netherlands), the SAL (a physician laboratory foundation in Utrecht and Groningen), and from the Dutch population which contacted the departments on their own after reading an article about the avoidance project in the media in the period 1996-2000. Participating centres were the Allergology departments of the University Hospitals of Groningen and Rotterdam and the Dermatology department of the University Hospital Utrecht. The Medical Ethics Committees of all Three University Hospitals approved the study and all patients gave written informed consent. Patients visited the clinic for baseline measurements on two consecutive days for tests. Patients who were included had at least a specific IgE level ≥ 0.7 kU/l for Der p1 or a class I positive pricktest for Der p1 (10.000 Bu/ml, ALK-ABELLO, Spain). The specific inclusion and exclusion criteria are stated in Table 1.

Table 1: In- and exclusion criteria

Inclusion criteria	Exclusion criteria
1 Atopic dermatitis 2 RAST class 2 and/or skin test index ≥ 0.7 3 Der p1 or f1 ≥ 200 ng/g dust in the dust sample of the mattress 4 no encasings or willing to remove them for the period of the study	1 Pets at home and positive skin test (index ≥ 0.7) and/or RAST ≥ class 2 for the pet 2 pregnant or lactating 3 daily use of oral steroids 4 daily use of cyclosporine

Antihistamine drugs and class 2 topical steroids were allowed between the test periods. AD patients with or without allergic asthma (AA) or allergic rhinitis (AR) were permitted to the study, if they met the criteria of Hanifin and Rajka.[16] In addition, to ensure that subjects did have active AD a score system was used. We used the Leicester sign score (LSS) for AD divided in a severity and extent score.[17]Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification) generated a total body disease activity score, the LSS severity score (with minimum 0 and maximum 108). Extent of the disease was assessed according to the "rule of nines" and resulted in the LSS extent score (with minimum 0 and maximum 100 %). Also a composite score was created called LSS composite by multiplying LSS severity with LSS extent. A LSS of at least 1-% extent and 6 point's severity was required.

Study design

The study was a randomised double-blind, placebo-controlled trial of 12 months duration, the active treatment (the mattress encasing group) consisted of Goratex bedding system (HAL, Haarlem, the Netherlands). The placebo group were given cotton encasings (HAL, Haarlem, the Netherlands). The encasings were applied to the mattress, duvet and pillows on all beds in the patient's room. Patients contacted our clinics at three moments at starting point (T0), after four months (T4) and after twelve months (T12).

Dust sampling

Dust samples were collected over five minutes from a one square meter area with a vacuum cleaner (Rowenta RS 005 Dymbo, 1200 Watt) containing a 20 μm filter paper in a filter chamber by a blinded study nurse (ALK, the Netherlands). Dust was sampled before treatment, at 4 months and at 12 months from the mattress and floor of the patient's bedroom and from the living room. Dust samples were weighed and stored at –18 ° C until extracted. Der p 1 was measured by a competitive radioimmunoassay as described for grass pollen allergen.[18] For this assay, 50 μl (of a dilution of) the dust extract was incubated at room temperature with 50 μl of a 1/2500 dilution of a rabbit anti-D.pteronyssinus antiserum. After 2 hrs 1 ng 125I-labelled affinity-purified Der p 1 and 0.5 mg Sepharose-coupled Protein A was added. The final reaction volume was 400 μl. After overnight incubation on a mixer, Sepharose-bound radioactivity was measured. The results were compared with an in-house

reference calibrated against the WHO reference, assuming that one international unit equals 0.125 ng. The lower limit of detection of this assay is 0.5 ng/ml.

Assessments

QoL was also measured with a generic questionnaire, the SF-36, We used the translation of Aaronson of the MOS SF-36[19], originally developed by Ware and co-workers. [12-15] SF-36 consists of 36 questions covering eight subscales, representing both a physical and a mental health summary component. Physical health subscales are physical functioning (PF), role physical functioning (RP), bodily pain (BP) and general health (GH); mental health subscales are mental health (MH), role mental functioning (RE), social functioning (SF) and vitality (VT). Questions are stated in both yes/no form and multiple choice. Sum score is calculated for each subscale and transformed to a percentage of the total possible score. The physical component summary (PCS) consists of PF, RP, BP, GH and the mental component summary (MCS) consists of MH, RE, SF and VT. High score indicates good QoL, whereas low score indicates low quality of life.[12-15;20] The reliability in two general populations samples as reported by Aaronson using Cronbach's alpha varied from 0,76 to 0,92 while the item discriminant validity varied from 0,09 to 0,64. For RRM we used the untransformed PCS and MCS.

Statistical Analysis

Data were analysed using Statistical Analysis Systems (SAS) statistical program. Means and standard deviations represented the levels and the dispersions of the data, respectively.
To analyse longitudinal data Random regression modelling (RRM) for continuous data was applied. RRM is a highly flexible and proper approach for repeated measurements.[21-24]RRM enables to model change across time and at both group and individual level. The qualities of RRM above and beyond to multivariate analysis of variance for repeated measurements is that RRM is not restricted to modelling time as a fixed effect; on the contrary, in RRM both the number of measurements across time and the moment of measurement may vary. Time-constant and time-varying variables can be entered in RRM. The structural form of the within subject covariance matrix of MANOVA for repeated measurements is assumed to meet the criteria of 'compound symmetry', that is to say that the variances and covariances are assumed to be constant across time. RRM, however, is utmost flexible in that variances and covariances across time may assume other kinds of error structure. In this study it is assumed to be unstructured (fully parameterised). In addition, RRM can handle missing data if the missing of data can be assumed to missing at random.[25] This implies that patients who were missing at a given measurement moment, were not excluded from analyses. [21-24]

The analysis strategy was as follows: first, the variables linear time trend, activity of AD situated at different body parts, treatment, log concentration Der p1 + Der f1, age and gender were entered as fixed terms into the model, and only the intercept was assumed to be random. Second, the interaction of quadratic time trend was added to the first model. The third model comprised the first model with the interaction of linear time trend and treatment with a random intercept. The fourth model was the third model with quadratic time trend. The

foregoing model added with the interaction of quadratic time trend and treatment formed the fifth model. The next five models were identical to the first five models, respectively, but differed from them in that the linear time trend was introduced as a random term. The last five models were also identical to the first five but had three random terms intercept, linear time trend and quadratic time trend. Altogether, it was attempted to identify fifteen models.

Regarding overall measure of model fit, the likelihood statistic becomes larger as more parameters are added to the model. Two statistics based on the likelihood of model fit and making allowance for the number of covariance parameters fitted are the Akaike's information criterion (AIC) and Schwarz's information criterion (SIC).[26] Models with larger values of AIC and SIC denote better fit.

Models can also be compared statistically using likelihood ratio test provided that they fit the same fixed effects and their covariance parameters are nested.[26;27]} Nesting of covariance parameters occurs when the covariance parameters in the simpler model can be obtained by restricting some of the parameters in the more complex model. The likelihood ratio test statistic is given by

$$2\,(\log(L_1) - \log(L_2)) \sim X^2_{DF}$$

where DF=difference in number of covariance parameters fitted. The models were selected by first statistically test for fixed effects of the models using the difference of –2 restricted loglikelihood ratios for the respective models along with the difference in corresponding degrees of freedom. And thereafter testing for random which runs as follows: the p-values of the models with degrees of freedom belonging to the respective models were averaged.

Results

General Results

Sixty-four patients with AD were included, 33 were allocated to the placebo group and 31 patients to the active treatment group (see figure 1). Two patients dropped out before four months, one due to moving; the other found the project to tedious. Six patients dropped out between four and twelve months. One started using class three steroids, one found the encasing too hot, two patients became pregnant, one moved and one stopped of unknown reasons.

In Table 2 the general characteristics of the population are presented. In Table 3 the univariate statistics of the outcome variables are presented at the different time points. The proportional change of Der p1 + Der f1 at T4 compared with T0 and T12 compared with T0 is presented in figures 2 and 3. There is no significant decrease in the active treatment group.

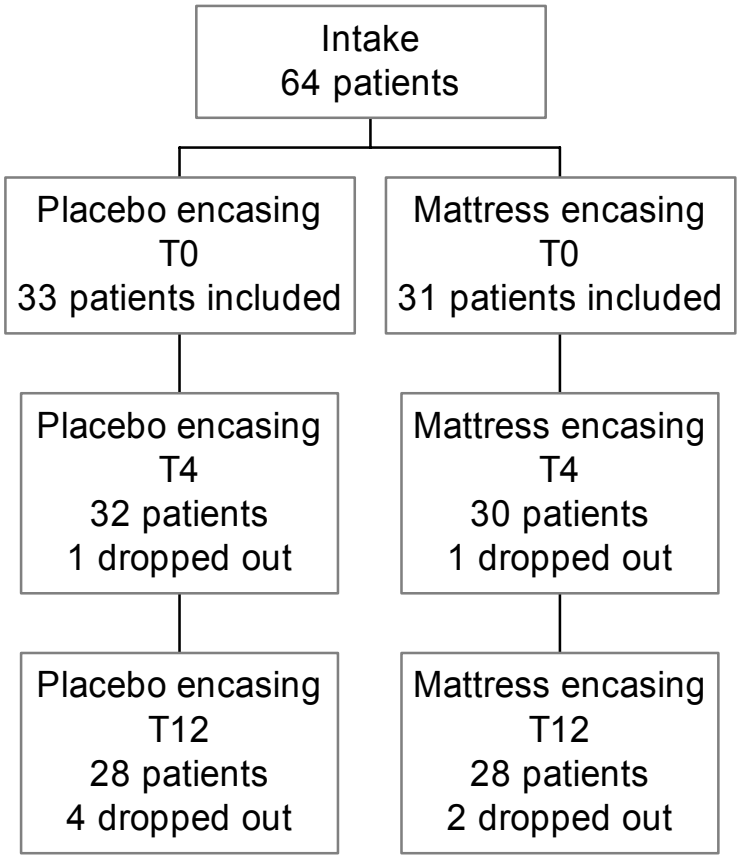

Figure 1: Inclusion, exclusion and dropping out of patients who were randomly allocated among both treatment groups.

Table 2: General characteristics of the population

	Placebo treatment n=33	Active treatment n=31
Age ($\bar{x}$, s)in years	30.6 (7.4)	28.9 (7.6)
AD (n)	2	5
AD + AR (n)	10	10
AD + AA (n)	2	0
AD + AA + AR (n)	19	16
Gender (m:f)	10:23	12:19
LSS severity (median, range)	16 (6-53)	18 (8-70)
LSS extent % (median, range)	26 (2-87)	24 (3-88)
LSS composite (median, range)	429 (14-2544)	400 (33-5280)

AD=Atopic Dermatitis
AA=Allergic Asthma
AR=Allergic Rhinitis

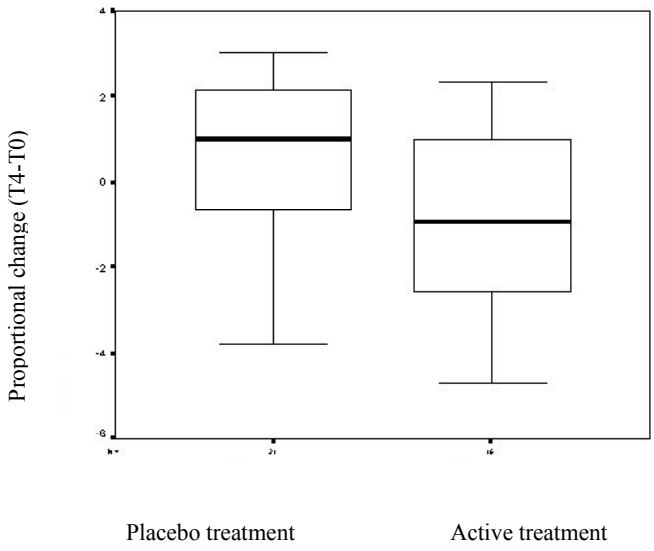

Figure 2: Proportional change of Der p1 + Der f1 concentration at T4 compared with T0 ((T4 Ln [Der p1 + Der f1])-(T0 Ln [Der p1 + Der f1])).

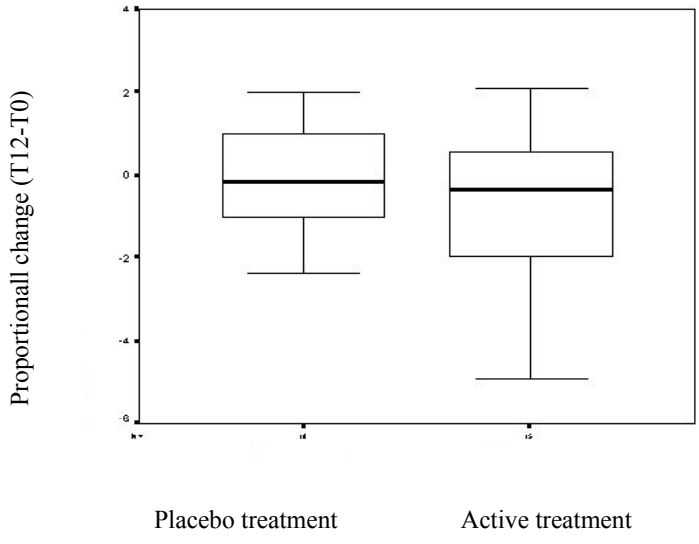

Figure 3: Proportional change of Der p1 + Der f1 concentration at T12 compared with T0 ((T12 Ln [Der p1 + Der f1])-(T0 Ln [Der p1 + Der f1])).

Table 3: Univariate statistics of outcome variables

	T0	**T4**	**T12**
Placebo treatment			
LSS composite (median, range)			
Head	30 (0 to 90)	12 (0 to 117)	21 (0 to 108)
Trunk	12 (0 to 270)	6 (0 to 330)	0 (0 to 360)
Arms	30 (0 to 252)	18 (0 to 216)	30 (0 to 216)
Legs	6 (0 to 108)	12 (0 to 180)	7.5 (0 to 195)
Total	429 (14 to 2544)	270 (0 to 6300)	354 (0 to 4140)
SF-36 (0-100 %)($\bar{x}$, s)			
PF	83.5 (15.7)	88.4 (11.0)	86.4 (15.6)
RP	72.7 (33.9)	84.7 (27.9)	83.0 (31.2)
GH	60.0 (20.7)	64.0 (20.8)	67.3 (18.4)
BP	78.0 (18.3)	81.1 (17.1)	80.9 (19.4)
SF	81.4 (16.3)	84.7 (16.0)	87.1 (16.5)
VT	61.1 (19.6)	64.7 (15.5)	63.8 (19.1)
MH	79.0 (15.4)	77.2 (13.7)	78.9 (15.0)
RE	84.8 (32.4)	92.5 (16.6)	88.1 (29.0)
PCS	73.6 (17.1)	79.5 (15.3)	79.4 (17.1)
MCS	76.6 (16.5)	79.7 (11.2)	79.4 (17.3)
Active treatment			
LSS composite (median, range)			
Head	27 (0 to 108)	24 (0 to 81)	12 (0 to 99)
Trunk	6 (0 to 300)	0 (0 to 288)	0 (0 to 180)
Arms	36 (0 to 192)	30 (0 to 144)	14 (0 to 234)
Legs	18 (0 to 165)	18 (0 to 90)	3 (0 to 120)
Total	400 (33 to 5280)	280.5 (0 to 3240)	216 (0 to 3300)
SF-36 (0-100 %) ($\bar{x}$, s)			
PF	86.9 (13.5)	90.5 (11.4)	89.6 (10.6)
RP	85.5 (24.8)	79.3 (35.4)	84.8 (26.6)
GH	63.0 (21.9)	64.6 (20.1)	66.9 (19.5)
BP	78.2 (23.0)	82.6 (18.2)	84.6 (17.2)
SF	82.7 (21.3)	81.0 (19.7)	89.7 (14.9)
VT	63.4 (21.3)	61.7 (17.7)	67.1 (19.4)
MH	78.3 (12.8)	71.9 (15.2)	81.6 (11.5)
RE	92.5 (18.7)	71.3 (41.5)	89.3 (24.1)
PCS	78.4 (15.9)	79.5 (17.3)	81.5 (15.0)
MCS	79.2 (13.5)	71.5 (18.8)	81.9 (13.1)

Repeated measures modelling

The models with fixed and random effects of 'PCS' are presented in Table 4. No model was statistically better than the simple (first) model. Adding random coefficients linear time and linear time combined with quadratic time next to random intercept did not improve the model fit (X^2 =1.66, p=0.32 and X^2 =1.82, p=0.39, respectively).

Table 4: Summary of the results of fitting different covariance models to the QCSD data.

Model	AIC	SBC	-2L REML
'PCS' random intercept			
Main effects	-268.38	-273.28	536.76
Main effects with ttime	-269.65	-272.55	535.30
Main effects with treatm*time	-271.28	-274.18	538.57
Main effects with ttime + treatm*time	-270.55	-273.44	537.11
Main effects with ttime + treatm * time + treatm * ttime	-271.12	-274.00	538.23
'PCS' random intercept, time			
Main effects	-271.55	-277.36	535.10
Main effects with ttime	-270.94	-276.74	533.88
Main effects with treatm*time	-272.43	-278.23	536.87
Main effects with ttime + treatm*time	-271.82	-277.60	535.64
Main effects with ttime + treatm * time + treatm * ttime	-272.40	-278.16	536.79
'PCS' random intercept, time, ttime			
Main effects	-274.47	-284.64	534.94
Main effects with ttime	-273.77	-283.91	533.53
Main effects with treatm*time	-275.33	-285.48	536.67
Main effects with ttime + treatm*time	-274.60	-284.71	535.19
Main effects with ttime + treatm * time + treatm * ttime	-275.20	-285.29	536.40

The polynomial models of 'MCS' are presented in Table 5. No model was statistically better than the simple (first) model. Adding random coefficients linear time next to random intercept did not improve the model fit (X^2 =0.09, p=0.86 and X^2 =0.77, p=0.62, respectively).

Table 5: Summary of the results of fitting different covariance models to the QCSD data.

Model	AIC	SBC	-2L REML
'MCS' random intercept			
Main effects	-295.14	-298.05	586.28
Main effects with ttime	-294.78	-297.69	585.56
Main effects with treatm*time	-295.73	-298.64	587.47
Main effects with ttime + treatm*time	-295.39	-298.29	586.79
Main effects with ttime + treatm * time + treatm * ttime	-293.77	-296.66	583.54
'MCS' random intercept, time			
Main effects	-297.10	-302.92	586.19
Main effects with ttime	-296.69	-302.50	585.39
Main effects with treatm*time	-297.68	-303.49	587.35
Main effects with ttime + treatm*time	-297.29	-303.08	586.58
Main effects with ttime + treatm * time + treatm * ttime	-295.59	-301.37	583.18
'MCS' random intercept, time, ttime			
Main effects	-299.75	-309.95	585.51
Main effects with ttime	-299.40	-309.57	584.80
Main effects with treatm*time	-293.01	-300.01	586.01
Main effects with ttime + treatm*time	-299.73	-309.87	585.45
Main effects with ttime + treatm * time + treatm * ttime	-297.94	-308.05	581.87

The results of the best models of random regression modelling are presented in Table 6 and 7. 'PCS' is specified by three significant covariates: linear time, log trunk LSS composite score and log arms LSS composite score (equation: PCS (5.25-18.75)=17.02 + 0.16 time (months) – 0.43 log trunk LSS – 0.42 log arms LSS composite. 'MCS' is specified by the two covariates: log trunk LSS composite and log arms LSS composite (equation MCS (3.5-17.5)=16.18 – 0.49 log trunk LSS composite – 0.61 log arms LSS composite.

Table 6: Random regression modelling results for 'PCS'

	Estimate	Standard Error	p-value
Intercept	17.02	1.31	**0.0001**
Slopes			
linear time	$1.64\ 10^{-1}$	$6.72\ 10^{-2}$	**0.0164**
gender	$5.58\ 10^{-1}$	$5.43\ 10^{-1}$	0.3080
age	$-2.84\ 10^{-2}$	$3.15\ 10^{-2}$	0.3702
treatment	$3.76\ 10^{-1}$	$4.65\ 10^{-1}$	0.4202
log head LSS severity	$2.41\ 10^{-1}$	$2.16\ 10^{-1}$	0.2687
log trunk LSS severity	$-4.26\ 10^{-1}$	$1.61\ 10^{-1}$	**0.0100**
log arms LSS severity	$-4.18\ 10^{-1}$	$1.99\ 10^{-1}$	**0.0395**
log legs LSS severity	$-2.43\ 10^{-2}$	$1.55\ 10^{-1}$	0.8762
log (Der p1 + Der f1)	$-9.97\ 10^{-3}$	$6.64\ 10^{-2}$	0.8811

Table 7: Random regression modelling results for 'MCS'

	Estimate	Standard Error	p-value
Intercept	16.18	1.35	**0.0001**
Slopes			
linear time	$9.61\ 10^{-2}$	$9.34\ 10^{-2}$	0.3066
gender	1.09	$5.12\ 10^{-1}$	0.0363
age	$-1.05\ 10^{-2}$	$2.90\ 10^{-2}$	0.7189
treatment	$-1.58\ 10^{-2}$	$4.29\ 10^{-1}$	0.9707
log head LSS severity	$-1.08\ 10^{-1}$	$2.73\ 10^{-1}$	0.6924
log trunk LSS severity	$-4.94\ 10^{-1}$	$2.02\ 10^{-1}$	**0.0167**
log arms LSS severity	$-6.10\ 10^{-1}$	$2.52\ 10^{-1}$	**0.0181**
log legs LSS severity	$-7.67\ 10^{-2}$	$2.04\ 10^{-1}$	0.7081
log (Der p1 + Der f1)	$-9.56\ 10^{-2}$	$8.41\ 10^{-2}$	0.2590

Discussion

We report for the first time a relation between AD present at specific body sites and impact on QoL, measured by a generic quality of life instrument, the SF-36. The SF-36 comprises two summary factors, the physical (PCS) and mental (MCS) component score, these were used for analysis. It appeared that the PCS is specified by three covariates: AD localised on the trunk and arms, which have a negative, and time which has a positive effect. The MCS is specified by AD present at trunk and arms, which both have a negative effect. Because AD is easily visible at arms and head by patients and their environment, we hypothesised that presence of AD at these sites would have a severe negative effect on MCS. While taking in account the larger body area of trunk and legs these covariates might have a more profound effect on PCS.

However, having AD at the head did not influence MCS, probably because patients could not see the severity of AD themselves, in contrast to AD present at arms and trunk (chest).
As expected, AD present at the trunk has a negative effect on PCS, while time has a positive effect. Passing of time results in an independent improvement of PCS probably caused by adaptation to the present situation. This observation reveals also one of the weak points of quality of life measurements, patients perceptions may shift in time independent of their disease severity, leading to a different relation between clinical aspects of a disease and quality of life in time.

In this model no effects of treatment, gender, age or concentration of Der p1 + Der f1 was seen. We evaluated in an earlier study the effect of encasing in a group with more parents where children also were included. Despite significant decrease in Der p1 + Der f1 concentration no clinical effect was observed. This study shows that applying encasings and decreasing the house dust mite concentration does not lead to a better QoL. While having AD at both arms, and trunk and arms results in an impairment of PCS and MCS, respectively.

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Chapter 8

Longitudinal double-blind placebo controlled study of effect of mattress encasings, house dust mite and Atopic Dermatitis on disease specific quality of life

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Submitted

Longitudinal double-blind placebo controlled study of effect of mattress encasings, house dust mite and Atopic Dermatitis on disease specific quality of life

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Summary
Background: Atopic Dermatitis (AD) can have a profound effect on quality of life (QoL). Several studies have already assessed QoL in AD, but there is still not much knowledge about how change of clinical (classical) parameters emanates in change of QoL parameters.
Objective: To analyze to what extent site and severity of AD influences disease specific QoL and if it is affected by exposure to HDM, age, gender and treatment with mite-impermeable encasings.
Methods: AD patients (18-50 years) who were allergic to house dust mite (HDM) and did have a Leicester Sign Score (LSS, a dermatitis score) of at least 1 % extent and a severity score of 6 points, were randomly allocated to an active (n=31) or a placebo allergen-avoidance group (n=33). Avoidance measures consisted of applying HDM-impermeable covers for mattresses, pillows, duvets and cotton covers for the placebo group. Effect on the allergen concentrations (Der p1 + Der f1), LSS extent and severity and disease specific Quality of Life as measured with the Questionnaire of coping with skin diseases (QCSD) and yielding two factors 'Feeling hurt' and 'Emotional distress' were studied.
Results : The decrease of Der p1 + Der f1 was not significant in the treatment AD group after applying avoidance measures for four and twelve months. The disease specific QoL factors 'Feeling hurt' is specified by three covariates, two body site specific AD scores (arms and trunk) and time. The factor 'Emotional distress' is specified by the body site specific arms AD score.
Conclusions: This study reports for the first time a relation between presence of AD on specific sites of the body and effect on disease specific QoL. Active AD at the arms can be easily seen, by patients themselves and their environment, and has a profound effect on 'Feeling hurt' and 'Emotional distress'. Having AD at the trunk has only an effect on perception of 'Feeling hurt' and not on 'Emotional distress', probably because the latter is more independent of severity and extent of visible AD. 'Feeling hurt' has also a negative time covariant, meaning that independently from disease severity a later time point results in a better QoL. It is possible that in time patients are getting used to living with AD.

Keywords : Atopic dermatitis, quality of life, questionnaire, Leicester Sign Score, house dust mite, longitudinal analysis, body site specific, double-blind placebo controlled

Abbreviations
AA: Allergic asthma
AD: Atopic dermatitis
AR: Allergic rhinitis
HDM: House dust mite
LSS: Leicester sign score
QCSD: Questionnaire of coping with skin diseases
QoL: Quality of life

Introduction

Atopic Dermatitis is a skin disease, which can have a large impact on QoL.[1-3] Patients are aware that their environment can see and react to their symptoms of erythema, scaling, lichenification and other symptoms. Sensations of itching and pain could lead to feelings of impairment and emotional distress. Treatment of AD comprises patient education and pharmacotherapy. In recent years, attention has been focused on the effect of environmental control. Several studies showed a beneficial effect of house dust mite avoidance measures like mattress, pillow and duvet encasings on improvement of AD.[4-7] One might expect that improvement of AD lead to improvement of QoL. Experienced improvement of QoL by patients due to treatment might lead to better compliance in the long run, so it is important to measure QoL, not only to evaluate the impact of AD on QoL, but also to assess the efficacy of medical interventions.

QoL questionnaires may deal with both disease-specific quality of life and general quality of life. Different dermatology specific measures have been developed and used in randomized controlled trials. These include the Dermatology Life Quality Index (DLQI)[8], Questionnaire of Coping with Skin diseases (QCSD)[9-11], Skinindex[12], Dermatology Quality of Life Scales (DQLS)[13] and Dermatology Specific Quality of Life[14]. The disease specific questionnaires are more sensitive to change. Recently, we validated the QCSD, which comprises two relevant dimensions 'Feeling hurt', and 'Emotional distress' and used it in this study.

Although the importance of quality of life has been acknowledged and assessment of quality of life has been frequently included as outcome measure in randomized clinical trials, there is not much knowledge about change of QoL parameters emanating from change of clinical (classical) parameters. It is expected that amelioration or deterioration of AD corresponds with greater, respectively lesser impairment in disease-specific quality of life. Even if this is the case, we do not know which aspects of AD really bother patients thereby influencing disease specific quality of life. Therefore, the primary objective of the study is to test to what extent site and severity of AD influences QoL. In addition, by testing these effects longitudinally within the context of a randomize clinical trial to the effects of encasings in AD, we were able to address the question whether disease specific QoL is affected not only by disease severity but also by exposure to HDM, age, gender and above all by treatment with mite-impermeable encasings.

Material and methods

Patients

Patients with AD aged between 18 and 50 years were recruited from the dermatology, Allergology and pulmonary outpatient clinic at the University Hospital in Utrecht, Rotterdam and Groningen (the Netherlands), the SAL (a physician laboratory foundation in Utrecht and Groningen), and from the Dutch population which contacted the departments on their own after reading an article about the avoidance project in the media in the period 1996-2000.

Participating centres were the Allergology departments of the University Hospitals of Groningen and Rotterdam and the Dermatology department of the University Hospital Utrecht. The Medical Ethics Committees of all Three University Hospitals approved the study and all patients gave written informed consent. Patients visited the clinic for baseline measurements on two consecutive days for tests. Patients who were included had at least a specific IgE level ≥ 0.7 kU/l for Der p1 or a class I positive pricktest for Der p1 (10.000 Bu/ml, ALK-ABELLO, Spain). The specific inclusion and exclusion criteria are stated in Table 1.

Table 1: In- and exclusion criteria

Inclusion criteria	Exclusion criteria
1 Atopic dermatitis 2 RAST class 2 and/or skin test index ≥ 0.7 3 Der p1 or f1 ≥ 200 ng/g dust in the dust sample of the mattress 4 no encasings or willing to remove them for the period of the study	1 Pets at home and positive skin test (index ≥ 0.7) and/or RAST ≥ class 2 for the pet 2 pregnant or lactating 3 daily use of oral steroids 4 daily use of cyclosporine

Antihistamine drugs and class 2 topical steroids were allowed between the test periods. AD patients with or without allergic asthma (AA) or allergic rhinitis (AR) were permitted to the study, if they met the criteria of Hanifin and Rajka.[15] In addition, to ensure that subjects did have active AD a score system was used. We used the Leicester sign score (LSS) for AD divided in a severity and extent score. [6;16] Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification) generated a total body disease activity score, the LSS severity score (with minimum 0 and maximum 108). Extent of the disease was assessed according to the "rule of nines" and resulted in the LSS extent score (with minimum 0 and maximum 100 %). Also a composite score was created called LSS composite by multiplying LSS severity with LSS extent. A LSS of at least 1% extent and 6 point's severity was required.

Study design

The study was a randomised double-blind, placebo-controlled trial of 12 months duration, the active treatment (the mattress encasing group) consisted of Goratex bedding system (HAL, Haarlem, the Netherlands). The placebo group were given cotton encasings (HAL, Haarlem, the Netherlands). The encasings were applied to the mattress, duvet and pillows on all beds in the patient's room. Patients contacted our clinics at three moments at starting point (T0), after four months (T4) and after twelve months (T12).

Dust sampling

Dust samples were collected over five minutes from a one square meter area with a vacuum cleaner (Rowenta RS 005 Dymbo, 1200 Watt) containing a 20 μm filter paper in a filter chamber by a blinded study nurse (ALK, the Netherlands). Dust was sampled before

treatment, at 4 months and at 12 months from the mattress and floor of the patient's bedroom and from the living room. Dust samples were weighed and stored at –18 ° C until extracted. Der p 1 was measured by a competitive radioimmunoassay as described for grass pollen allergen.[17] For this assay, 50 µl (of a dilution of) the dust extract was incubated at room temperature with 50 µl of a 1/2500 dilution of a rabbit anti-D.pteronyssinus antiserum. After 2 hrs 1 ng 125I-labelled affinity-purified Der p 1 and 0.5 mg Sepharose-coupled Protein A was added. The final reaction volume was 400 µl. After overnight incubation on a mixer, Sepharose-bound radioactivity was measured. The results were compared with an in-house reference calibrated against the WHO reference, assuming that one international unit equals 0.125 ng. The lower limit of detection of this assay is 0.5 ng/ml.

Assessments

QoL was measured using an AD specific questionnaire, the QCSD. The QCSD was translated from German to Dutch.[10;11;18] It is a 42-item self-administered survey instrument intended for AD. We recently analyzed the questionnaire, which yielded two orthogonal principal factors, labeled as ' Feeling hurt' and 'Emotional distress', comprising 9 and 7 items, respectively. A high score, range 1-5, indicates a low QoL whereas a low score indicates a good QoL. These two factors were used for analysis.

Statistical Analysis

Data were analysed using Statistical Analysis Systems (SAS) statistical program. Means and standard deviations represented the levels and the dispersions of the data, respectively.
To analyse longitudinal data Random regression modelling (RRM) for continuous data was applied. RRM is a highly flexible and proper approach for repeated measurements.[19-22]RRM enables to model change across time and at both group and individual level. The qualities of RRM above and beyond to multivariate analysis of variance for repeated measurements is that RRM is not restricted to modelling time as a fixed effect; on the contrary, in RRM both the number of measurements across time and the moment of measurement may vary. Time-constant and time-varying variables can be entered in RRM. The structural form of the within subject covariance matrix of MANOVA for repeated measurements is assumed to meet the criteria of 'compound symmetry', that is to say that the variances and covariances are assumed to be constant across time. RRM, however, is utmost flexible in that variances and covariances across time may assume other kinds of error structure. In this study it is assumed to be unstructured (fully parameterised). In addition, RRM can handle missing data if the missing of data can be assumed to missing at random.[23] This implies that patients who were missing at a given measurement moment, were not excluded from analyses. [19-21]

The analysis strategy was as follows: first, the variables linear time trend, activity of AD situated at different body parts, treatment, log concentration Der p1 + Der f1, age and gender were entered as fixed terms into the model, and only the intercept was assumed to be random. Second, the interaction of quadratic time trend was added to the first model. The third model comprised the first model with the interaction of linear time trend and treatment with a random intercept. The fourth model was the third model with quadratic time trend. The

foregoing model added with the interaction of quadratic time trend and treatment formed the fifth model. The next five models were identical to the first five models, respectively, but differed from them in that the linear time trend was introduced as a random term. The last five models were also identical to the first five but had three random terms intercept, linear time trend and quadratic time trend. Altogether, it was attempted to identify fifteen models.

Two other statistics based on the likelihood of model fit and making allowance for the number of covariance parameters fitted are the Akaike's information criterion (AIC) and Schwarz's information criterion (SIC).[24] Models with larger values of –2 REML, AIC and SIC denote better fit.

Models can also be compared statistically using likelihood ratio test provided that they fit the same fixed effects and their covariance parameters are nested.[24;25] Nesting of covariance parameters occurs when the covariance parameters in the simpler model can be obtained by restricting some of the parameters in the more complex model. The models were selected by first statistically test for fixed effects of the models using the difference of –2 restricted loglikelihood ratios for the respective models along with the difference in corresponding degrees of freedom. And thereafter testing for random which runs as follows: the p-values of the models with degrees of freedom belonging to the respective models were averaged.

Results

General Results

Sixty-four patients with AD were included, 33 were allocated to the placebo group and 31 patients to the active treatment group (see figure 1). Two patients dropped out before four months, one due to moving; the other found the project to tedious. Six patients dropped out between four and twelve months. One started using class three steroids, one found the encasing too hot, two patients became pregnant, one moved and one stopped of unknown reasons. The decrease of Der p1 + Der f1 measured as proportional change at T4 compared with T0 and at T12 compared with T0 was not significant in both treatment groups (figure 2 and 3, respectively).

In Table 2 the general characteristics of the population are presented. In Table 3 the univariate statistics of the outcome variables are presented at the different timepoints.

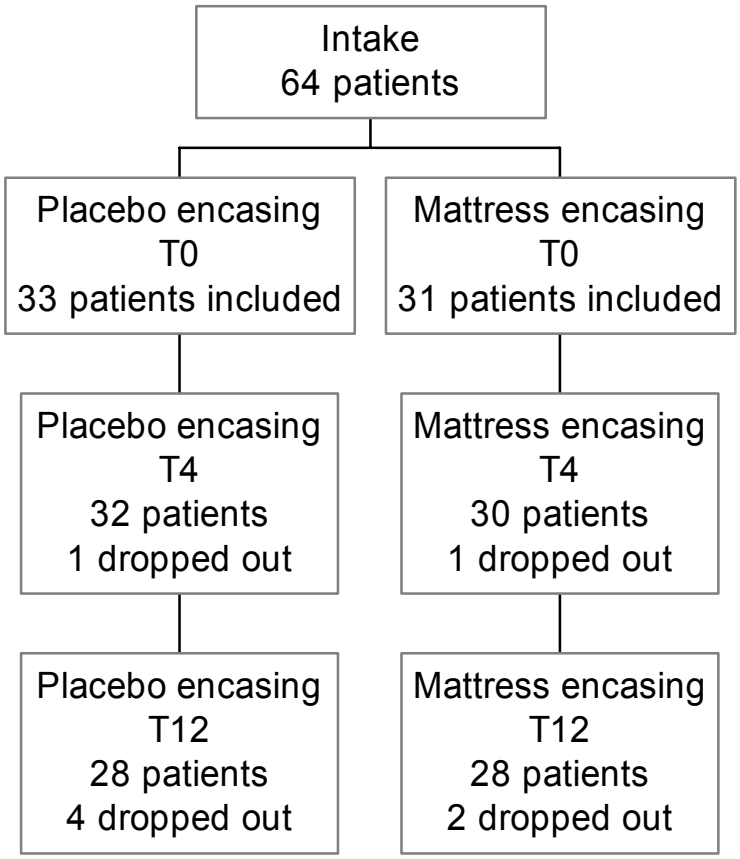

Figure 1: Inclusion, exclusion and dropping out of patients who were randomly allocated among both treatment groups.

Table 2: General characteristics of the population

	Placebo treatment n=33	Active treatment n=31
Age ($\bar{x}$, s) in years	30.6 (7.4)	28.9 (7.6)
AD (n)	2	5
AD + AR (n)	10	10
AD + AA (n)	2	0
AD + AA + AR (n)	19	16
Gender (m:f)	10:23	12:19
LSS severity (median, range)	16 (6-53)	18 (8-70)
LSS extent % (median, range)	26 (2-87)	24 (3-88)
LSS composite (median, range)	429 (14-2544)	400 (33-5280)

AD=Atopic Dermatitis
AA=Allergic Asthma
AR=Allergic Rhinitis

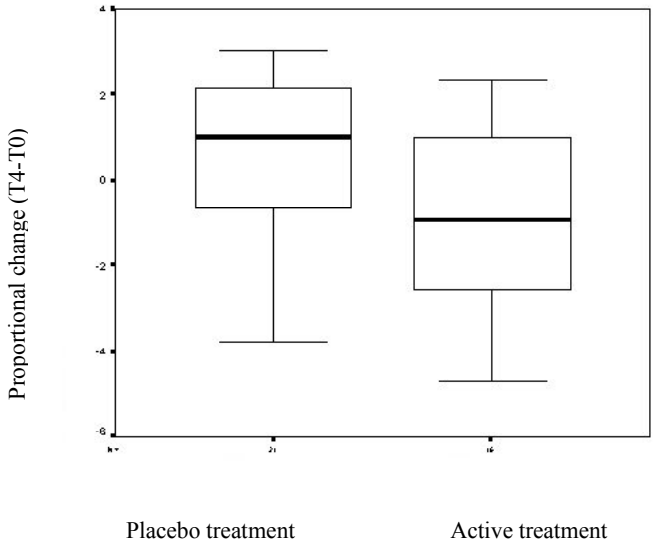

Figure 2: Proportional change of Der p1 + Der f1 concentration at T4 compared with T0 ((T4 Ln [Der p1 + Der f1])-(T0 Ln [Der p1 + Der f1])).

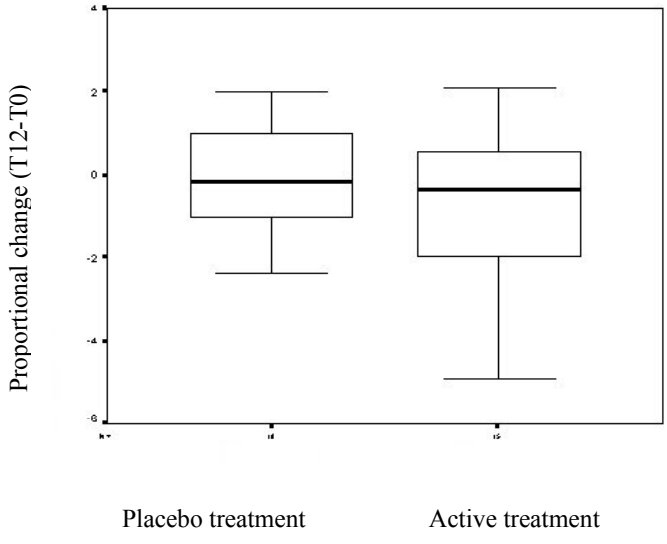

Figure 3: Proportional change of Der p1 + Der f1 concentration at T12 compared with T0 ((T12 Ln [Der p1 + Der f1])-(T0 Ln [Der p1 + Der f1])).

Table 3: Univariate statistics of outcome variables

	T0	**T4**	**T12**
Placebo treatment			
LSS composite (median, range)			
Head	30 (0 to 90)	12 (0 to 117)	21 (0 to 108)
Trunk	12 (0 to 270)	6 (0 to 330)	0 (0 to 360)
Arms	30 (0 to 252)	18 (0 to 216)	30 (0 to 216)
Legs	6 (0 to 108)	12 (0 to 180)	7.5 (0 to 195)
Total	429 (14 to 2544)	270 (0 to 6300)	354 (0 to 4140)
QCSD ($\bar{x}$, s)			
Feeling hurt	2.6 (0.8)	2.5 (0.9)	2.4 (0.9)
Emotional distress	2.4 (0.8)	2.4 (0.8)	2.2 (0.9)
Active treatment			
LSS composite (median, range)			
Head	27 (0 to 108)	24 (0 to 81)	12 (0 to 99)
Trunk	6 (0 to 300)	0 (0 to 288)	0 (0 to 180)
Arms	36 (0 to 192)	30 (0 to 144)	14 (0 to 234)
Legs	18 (0 to 165)	18 (0 to 90)	3 (0 to 120)
Total	400 (33 to 5280)	280.5 (0 to 3240)	216 (0 to 3300)
QCSD ($\bar{x}$, s)			
Feeling hurt	3.1 (0.9)	2.9 (0.8)	2.7 (0.8)
Emotional distress	2.3 (0.9)	2.3 (0.8)	2.1 (0.9)

Repeated measures modelling

The models with fixed and random effects of 'Feeling hurt' are presented in Table 4. All models were statistically better than the simple (first) model ($p < 0.05$) except the second model with quadratic time effect ($X^2_1=3.47$, $p=0.062$). The third model with linear time and treatment effect was significantly better than the first ($X^2_1=3.98$, $p<0.05$); the fourth model was not significantly better than the third model ($X^2_1=3.46$, $p=0.06$). Adding random coefficients linear time and linear time combined with quadratic time next to random intercept did not improve the model fit ($X^2=0.47$, $p=0.71$; $X^2=4.50$, $p=0.12$, respectively).

Table 4: Summary of the results of fitting different covariance models to the QCSD data.

Model	AIC	SIC	-2L REML
'Feeling hurt' random intercept			
Main effects	-145.63	-148.54	287.25
Main effects with ttime	-147.36	-150.27	290.72
Main effects with treatm*time	-147.61	-150.52	291.23
Main effects with ttime + treatm*time	-149.35	-152.24	294.69
Main effects with ttime + treatm * time + treatm * ttime	-151.04	-153.93	298.09
'Feeling hurt' random intercept, time			
Main effects	-147.40	-153.22	286.79
Main effects with ttime	-149.12	-154.93	290.23
Main effects with treatm*time	-149.38	-155.19	290.76
Main effects with ttime + treatm*time	-151.09	-156.88	294.17
Main effects with ttime + treatm * time + treatm * ttime	-152.81	-158.59	297.62
'Feeling hurt' random intercept, time, ttime			
Main effects	-148.63	-158.83	283.27
Main effects with ttime	-150.30	-160.46	286.59
Main effects with treatm*time	-150.39	-160.56	286.78
Main effects with ttime + treatm*time	-152.04	-162.18	290.08
Main effects with ttime + treatm * time + treatm * ttime	-13.76	-163.87	293.51

The polynomial models of 'Emotional distress' are presented in Table 5. All models were statistically better than the simple (first) model. The fourth model with quadratic time effect combined with linear time and treatment effect was also significantly better compared to the second (X^2_1=4.11, p=0.04); and third model (X^2_1=4.07, p=0.04). Adding random coefficients linear time next to random intercept did not improve the model fit (X^2=0.59, p=0.59), the model did not converge after adding random coefficients quadratic time next to intercept and linear time.

Table 5: Summary of the results of fitting different covariance models to the QCSD data.

Model	AIC	SIC	-2L REML
'Emotional distress' random intercept			
Main effects	-147.45	-150.36	290.90
Main effects with ttime	-149.49	-152.40	294.98
Main effects with treatm*time	-149.51	-152.42	295.02
Main effects with ttime + treatm*time	-151.55	-154.45	299.09
Main effects with ttime + treatm * time + treatm * ttime	-153.10	-155.99	302.21
'Emotional distress' random intercept, time			
Main effects	-149.14	-154.97	290.28
Main effects with ttime	-151.20	-157.01	294.40
Main effects with treatm*time	-151.19	-157.00	294.38
Main effects with ttime + treatm*time	-153.25	-159.05	298.50
Main effects with ttime + treatm * time + treatm * ttime	-154.81	-160.59	301.61
'Emotional distress' random intercept, time, ttime			
Main effects	d.n.c.*		
Main effects with ttime	-153.72	-163.89	293.44
Main effects with treatm*time	-153.70	-163.87	293.40
Main effects with ttime + treatm*time	d.n.c.*		
Main effects with ttime + treatm * time + treatm * ttime	d.n.c.*		

d.n.c.=did not converge

The results of the best models of random regression modelling are presented in Table 6 and 7. 'Feeling hurt' is specified by three covariates time, log LSS arms composite score, log LSS legs composite score (equation: 'Feeling hurt'(1-5) = 2.11 - 0.07 'time' (in months) + 0.13 'log trunk LSS composite' + 0.18 'log arms LSS composite'). 'Emotional distress' is specified by log LSS arms composite score (equation: 'Emotional distress'(1-5) = 1.69 + 0.33 'log arms LSS composite').

Table 6: Random regression modelling, results for 'Feeling hurt'

	Estimate	Standard Error	p-value
Intercept	2.11	$5.34\ 10^{-1}$	**0.0002**
Slopes			
linear time	$-6.98\ 10^{-2}$	$3.49\ 10^{-2}$	**0.0493**
linear time * treatment	$-1.93\ 10^{-2}$	$5.11\ 10^{-2}$	0.7069
gender	$-2.23\ 10^{-2}$	$2.24\ 10^{-1}$	0.9207
age	$-1.11\ 10^{-2}$	$1.30\ 10^{-2}$	0.3956
treatment	$3.97\ 10^{-1}$	$2.00\ 10^{-1}$	0.0514
log head LSS composite	$1.31\ 10^{-1}$	$8.43\ 10^{-2}$	0.1232
log trunk LSS composite	$1.25\ 10^{-1}$	$6.16\ 10^{-2}$	**0.0459**
log arms LSS composite	$1.81\ 10^{-1}$	$7.86\ 10^{-2}$	**0.0236**
log legs LSS composite	$4.92\ 10^{-2}$	$5.93\ 10^{-2}$	0.4087
log (Der p1 + Der f1)	$7.33\ 10^{-3}$	$2.60\ 10^{-2}$	0.7784

Table 7: Random regression modelling, results for 'Emotional distress'

	Estimate	Standard Error	p-value
Intercept	1.69	$5.55\ 10^{-1}$	**0.0034**
Slopes			
linear time	$5.60\ 10^{-2}$	$1.37\ 10^{-1}$	0.6841
quadratic time	$-2.67\ 10^{-2}$	$4.29\ 10^{-2}$	0.5361
linear time * treatment	$7.45\ 10^{-5}$	$5.13\ 10^{-2}$	0.9988
gender	$-2.73\ 10^{-1}$	$2.32\ 10^{-1}$	0.2427
age	$1.69\ 10^{-3}$	$1.35\ 10^{-2}$	0.9007
treatment	$-6.54\ 10^{-2}$	$2.07\ 10^{-1}$	0.7526
log head LSS composite	$-6.20\ 10^{-2}$	$8.67\ 10^{-2}$	0.4767
log trunk LSS composite	$5.49\ 10^{-2}$	$6.30\ 10^{-2}$	0.3861
log arms LSS composite	$3.27\ 10^{-1}$	$7.93\ 10^{-2}$	**0.0001**
log legs LSS composite	$4.65\ 10^{-3}$	$7.35\ 10^{-2}$	0.9497
log (Der p1 + Der f1)	$4.46\ 10^{-2}$	$2.62\ 10^{-2}$	0.0927

Discussion

The aim of this study was to estimate the different aspects of AD on disease specific quality of life. This study reports for the first time a relation between presence of AD on specific sites of the body and effect on QoL. The QoL instrument we used comprises two factors. It appeared that the factor 'Feeling hurt' is specified by AD localised at the trunk and the arms whereas the factor "Emotional distress" is associated with AD at the arms only.

We hypothesised skin disease involving head and arms would significantly influence QoL. AD patients might be aware that in general people could easily see AD at these parts. However, contrary to our expectations, having AD at the head was not a significant covariant in both dimensions. An explanation could be that patients do not see the severity of AD at this site themselves. In contrast to the presence of AD at the arms, which can be easily seen (especially when arms are uncovered by clothing) and having a significant influence on both factors. AD at the trunk only has an effect on 'Feeling hurt' and not on 'Emotional distress'. An explanation could be that perception of 'Feeling hurt' is more effected by the severity and extent of AD than 'Emotional distress' which could be more independent of the severity and extent of visible AD. 'Feeling hurt' has also a significant negative time covariant, meaning that – independently from disease severity - a later time point results in a lower 'Feeling hurt' score and a better QoL. It is possible that in time patients are getting used to living with AD. This type of analysis may reveal those aspects of skin disease that bother patients most. Such information can be important for the clinician to understand the patient in their management of disease. It can also be seen that time itself may influence quality of life irrespective of disease severity. The latter observation discloses one of the weaknesses of quality of life measurement. Perceptions of quality of life experienced by persons may shift in time. This may be a result of adaptation to and coping with disease. This may result in a dissociation between physical aspects of disease and perceived quality of life. In particular, if follow up in a clinical trial is long lasting response shifts may be important. To understand the relationship between disease and health related quality of life better, the next step would be to look at causal relationships. Neither with standard multivariate analysis of variance for repeated measurements nor random regression modelling it is possible to reveal causal relationships and to draw paths between variables. Other techniques such as structural equation modelling (SEM) are required.

No effects of treatment, gender, age or concentration of Der p1 + Der f1 was seen on both factors. This study was part of a larger trial. We included children and we assessed AD by classical outcome measures such as LSS and visual analogue scales. Also in this extended study we did not see an effect of encasings, even in the presence of significant reduction in allergen exposure (Oosting et al) Our results are in line with a recent observation that a decrease in concentrations house dust mite allergen (due to treatment effect) does not automatically lead to a decrease in severity and extent of AD.[26]

In conclusion, use of mattress, duvet and pillow covering and decreasing the concentration house dust mite does not lead to a better QoL. Having AD at certain body sites, which can be easily seen by the patients themselves, does lead to an impairment of QoL.

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Chapter 9

General discussion and summary

General discussion and summary

This thesis shows the results and patient characteristics of three studies. One study was part of the Dutch Mite Avoidance Study (DUMAS): Effectiveness and effect modification of encasings in house dust mite allergy. The two other studies were two different studies with asthmatic patients recruited from and performed at the asthma centre Heideheuvel. Patient recruitment of the Heideheuvel study took place in the same geographical region in the period 1995-1997; the DUMAS study in 1997 and 1998.

In the DUMAS study patients were selected by using questionnaires where particular atopical core questions were addressed, together with a positive intradermal test or skin prick test for house dust mite. Patients were diagnosed as having reported AR, AA and/or AD on basis of this questionnaire. Then patients were randomised and stratified by age and recruiting centre. After randomisation patients were tested for AA with lung function tests (methacholine, adenosine, histamine)[1]; for AR, using nasal provocation tests with HDM and the nasal-score[2]; and for AD, using the LSS[3;4] for symptom grading and disease extent together with tests for allergen load and immunological and quality of life (QoL) variables. A difference in diagnoses was made by using questionnaires solely (reported diagnoses) and using questionnaires in combinations with clinical tests (clinical diagnoses). A difference between reported and clinical diagnoses was found in 84 out of 325 patients (25.8 %)(Chapter 2). There was a reported atopical comorbidity of 235 out of 325 patients (72.3 %) and a clinical atopical comorbidity of 177 in 325 patients (54.4 %).

Chapters 3, 4 and 5 show the effects of encasings on clinical, immunological and QoL variables. There was a lack of improvement of AD and AA in the active treatment groups despite a significant decrease in Der p1 and Der p1 + f1 exposure.

Lack of clinical effect in the active treatment groups is difficult to explain. Low baseline concentrations of Der p1 or Der p1 + f1 could result in little change of HDM allergen levels after intervention. Higher and lower baseline concentrations of HDM were reported.[5-15]Recent Dutch studies reported comparable levels of Der p1 or Der p1 +f1. In the DUMAS AD group the baseline data Der p1 in the mattresses (841 and 945 ng per gram dust, placebo and treatment group respectively) are in the same range as earlier reported by Cloosterman et al.[16] So this lower concentration of Der p1 per gram dust might be representative for the Dutch population study.

The Der p1 geometric mean concentration in the mattress after twelve months intervention in the DUMAS AD study decreased to 446 ng Der p1 per gram dust and the Der p1 + f1 to 1319 ng per gram dust. Some high altitude studies reported lower geometric means for Der p1 + Der f1 of 360 ng per gram dust and 180 ng per gram dust for Der p1 in mattresses.[17;18] There seems to be some room for improvement left in the active treatment group in the DUMAS study, but it is doubtful if encasings alone can decrease the concentration of Der p1 + Der f1 to this extent.

Van Strien et al.[19] reported an allergen load in the placebo group of 1851 (607-3957) ng Der p1 + f1 per gram dust and in the active treatment group of 1676 (419-5609) ng Der p1 + f1 per gram dust before intervention, that decreased after twelve months intervention to 1676 (419-5602) ng per gram dust and 1018 (465-3179) ng per gram dust, respectively.

In the DUMAS AD population the baseline levels of Der p1 + f1 were in the same range (< 10.000 ng): 3388 (1913-6000) ng per gram dust in the placebo group and 4069 (2573-6437) ng per gram dust in the active treatment group, increasing to 3749 (1921-7315) in the placebo group and decreasing significantly to 1319 (851-2046) Der p1 + f1 ng per gram dust in the active treatment group after 12 months intervention.

Surprisingly, in both Heideheuvel studies the geometric mean values were above 15000 ng Der p1 per gram dust. Patients in the Heideheuvel study were recruited 2 years earlier than the patients in the DUMAS study. Whether the high Der p1 exposure could be explained by the recruiting period or by specific patient characteristics within these relatively small groups of AA patients (27 and 38 respectively) compared to the 77 patients of the AD DUMAS study and 157 patients of the Cloosterman study[16], is not clear.
Nevertheless, lowering the Der p1 in both Heideheuvel studies with a factor 10 did not lead to improvement of clinical symptoms in the active treatment group of AA (Chapter 4, 5).

Another reason why the decrease in allergen exposure did not result in clinical improvement might be that the sleeping period in which the decrease in concentration of Der p1 or Der p1 + Der f1 in mattress and bedroom is experienced is just a part of the total exposure time. Patients might still be exposed to higher HDM levels outside the bedroom. Also other allergens in- and outside the domestic environment might have aggravated and maintained AD. Reduction of allergens in other environments (working place, school, and outdoors) might be equally important to improve AD.

Decreasing the 'wrong' allergens could also cause the lack of clinical effect. Several studies showed that HDM is one of the most important risk factors of sensitisation and inducing atopic symptoms.[20-22] Grading of allergens according to the prevalence of sensitisation within a population with AR, AA and/or AD revealed the following prevalences: HDM 68.4 %; cat 66.7 %, grass-pollen (GP) 64.9 %; making cat allergen the second most important indoor allergen.[20] The independent risk odds ratios (OR (95 % CI)) for HDM were 2.19 (0.92-5.17); 8.07 (4.6-14.14); and 1.95 (1.04-3.66) for AR, AA and AD respectively.[20;22] A study performed by Carswell et al.[12] showed that applying encasings and acaracides in houses without cats lowers the cat allergen Fel d1 from 24 (0-2240) ng per m^3 to 0 (0-0) ng per m^3, using a Casella air sampler. In houses with cats and in the placebo group no decrease in Fel d1 was seen. In the AD DUMAS study population the Fel d1 allergens were not measured. In this population 52 out of 73 AD patients were sensitised to cats, 52 to dogs. No cats and/or dogs were allowed during the study when patients were sensitised to these allergens. Presence of Fel d1 allergen in the study group homes is likely, the study of Carswell et al.[12] suggests

however that together with the decrease of Der p1 + f1 the Fel d1 would also have decreased in the active treatment group.

Multiple triggers

Exacerbation of atopic diseases is a complex process. It requires interactions between genotype and environmental conditions. This thesis deals with allergen specific triggers. But other non-allergic triggers can play an important part. Triggers for AA for instance consists of cold air, hyperventilation, exercise, psychological stress, β-blockers, oesophageal reflux, viral airway infections, tobacco smoke, air pollution etc.[23] Non allergic triggers for AD are psychological stress, contact irritants, climate, microbial and fungal agents.[24;25] Allergens form a part of these multiple triggers cumulating to a particular threshold level or gradually increasing the AR, AA and/or AD symptoms dependent of the cumulative trigger load. Lowering the major trigger could initially lead to an improvement of clinical symptoms, but at the same time it increases the relative contribution of other triggers. Not dealing with these other triggers could stop further improvement of symptoms.

Effect of genotype and environment on phenotype

As already stated, atopic diseases could be caused by interaction of multiple genes and environmental factors. It is possible that three major areas concerning atopy, inflammation and organs (nose, lungs, skin) at gene level interact with each other and induce the atopic prone genotype, combined with environmental factors results in a particular atopic phenotype.[26] Figure 1 shows the current state of affairs concerning discovered gene clusters that are associated with atopy (genotype box). Three gene clusters are associated with at least two atopic phenotypes: 5q31-32[27-31]; 11q13[32;33]; 12q13-24[34;35]. These three gene clusters code for several proteins that regulate and control the immune response: interleukines; colony stimulating factors; interferon gamma, which are inflammation specific proteins, and the beta subunit of the high-affinity receptor for IgE which is an atopy specific protein.[26-36] Concerning organ (skin) specific genes, an association between psoriasis and AD genes has also been found.[37] Surprisingly, Becker et al.[36] showed that the same gene clusters were involved not only in atopic but also in autoimmune diseases. These diseases did not always map to the same loci within the same gene. Probably a delicate balance concerning activation of gene clusters is necessary to prevent either atopic or autoimmune diseases. These data suggests that rigorous allergen avoidance measures solely will have a limited effect on prevention and exacerbation of atopic diseases.

Also, multiple atopy inhibiting and inducing triggers in the environment can influence the balance between Th1 and Th2. Strachan reported for the first time a reciprocal relation between hay fever, hygiene and household size.[38] Other studies reported quickly thereafter that respiratory, gastrointestinal pathogens, the commensal flora of gastrointestinal tract and bacterial cell-wand products could regulate the allergic specific immune responses towards a Th1- and inhibiting a Th2- profile, e.g. “reset” the Th2 prone individuals to a common Th1 profile. Absence of particular bacterial and viral infections, due to more westernised hygienic conditions, could result in individuals with a Th2 (allergy-prone) profile, this was called the

hygiene hypothesis.[39-43;43-50] Not all viral and bacterial pathogens cause a Th1- profile. Respiratory syncytial virus (RSV) and lower respiratory infections are associated with an increase in asthmatic symptoms and a Th2-profile.[41;44;50] Figure 1 gives a summary of environmental Th1 and Th2 inducing triggers (environment box).

Looking at the protective effect of particular bacterial and viral infections, some authors stated that this effect could be used and that Th2 prone individuals should be vaccinated with Th1 inducing vaccines, for example vaccines derived from Mycobacterium strains. The only antituberculosis vaccine at the moment is based on live, attenuated Bacillus Calmette-Guerin-Mycobacterium bovis (BCG).[39;51]However, retrospective studies show conflicting results concerning atopy preventing effects of BCG vaccination.[39;52-55]
There is a delicate balance between Th2 and Th1 phenotypes. Several studies show that different autoimmune diseases like rheumatoid arthritis, insulin-dependent diabetes mellitus and multiple sclerosis are associated with a Th1 phenotype.[56] The presence of autoimmune diseases is associated with a lower prevalence of atopic phenotypes in some studies but not all.[57-61] Vaccine strategies which aim for a general Th1 phenotype can have an adverse effect with respect to auto-immune diseases. We have to keep the old adage in mind “Primum no nocere” (doing no harm).

While Th1 triggers in the first two years of life might prevent the development of the atopic phenotype, the effect on adult atopic patients could be different. The a-specific non allergic triggers induce chronic inflammation in adult AD patients, resulting in a Th1 response.[24;62] Prevention of Th2 triggers solely by avoiding environmental allergens could disturb the Th1 and Th2 balance resulting in an increase of AD symptoms by enhancing the chronic inflammation. However, decrease of HDM allergen did not result in an increase of clinical symptoms. Development of effective treatment regimes should be aimed at inhibiting both the acute (Th2) and chronic (Th1) allergic inflammation.

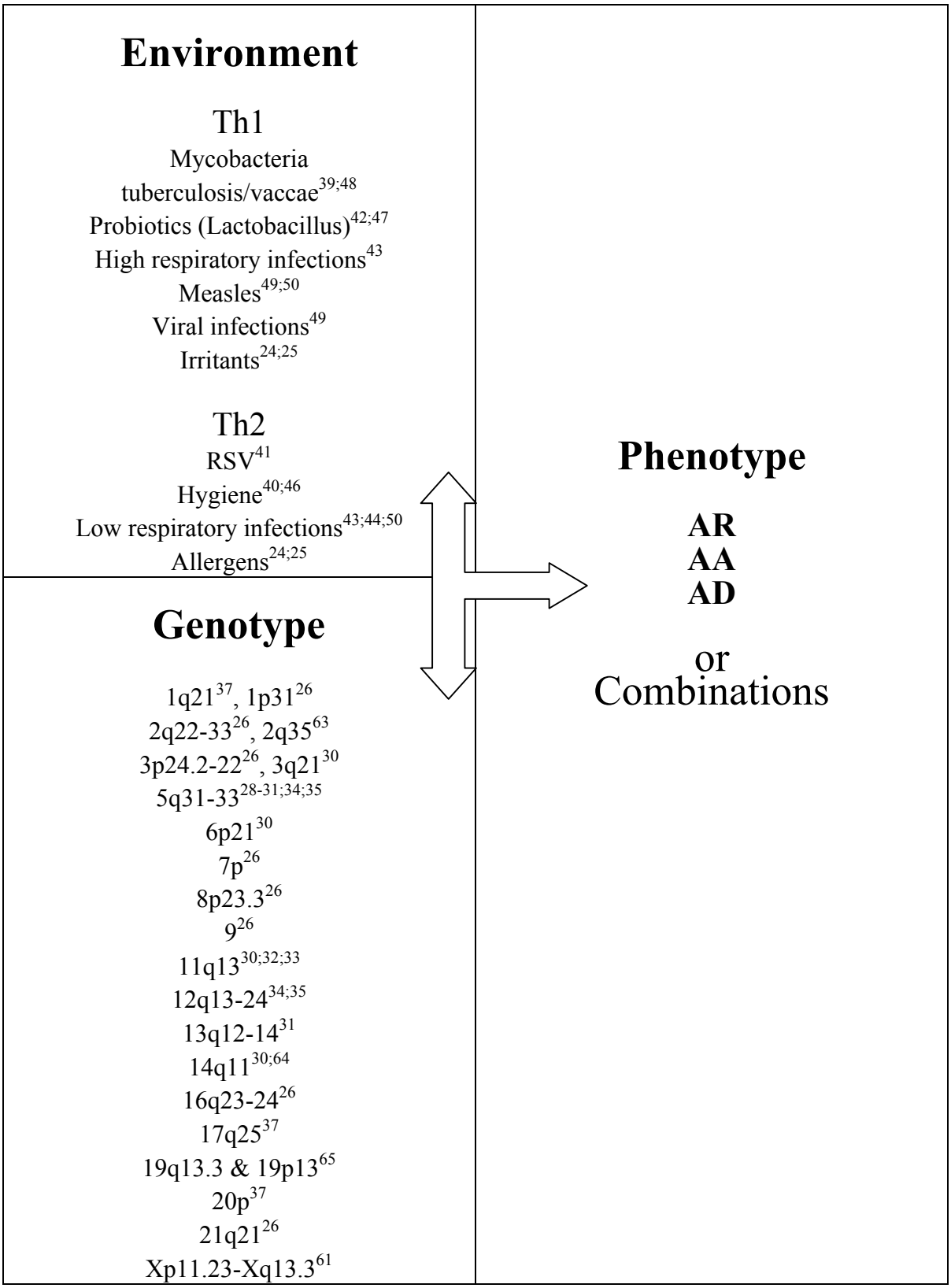

Figure 1: Interactions between genotype and environment resulting in a particular (combined) atopic phenotype.

Quality of life

Patient-assessed health outcomes can be divided in three categories: health status (health-related QoL and functional status); health utilities (patients' values for a particular state of health) and patient satisfaction. QoL is influenced by many factors such as financial status, housing, employment, social support network and health. QoL affected by health and health care, health-related QoL (HRQL) is often used in clinical research. The general QoL encompasses the HRQL.[66] Because no other QoL factors were assessed in this thesis, the term QoL is used for HRQL.

QoL becomes an important issue in evaluating effects of treatment in patients with chronic diseases. Several disease specific and generic questionnaires have been developed. Disease specific questionnaires assess the severity of particular disease specific (AA and AD) symptoms on patient's life[66] while generic questionnaires addresses the general "well being". Looking at the prevalence of atopic comorbidity within the selected populations, usage of both kinds of questionnaires is recommended (Chapter 5). The disease specific Quality of Life for Respiratory Illness Questionnaire (QoL-RIQ)[67] intended for AA and chronic obstructive pulmonary diseases (COPD) was used in the Heideheuvel study. Clinical relevant improvement in QoL was found in both groups and no difference between the active and placebo treatment groups was seen. Suggesting that it might rather reflect the special attention the patients received during the study period. The disease specific Questionnaire of Coping with Skin Diseases (QCSD)[68-71] was used for AD, together with the generic SF-36[72-75] questionnaire in the DUMAS study. The QCSD could be condensed to a 16 items questionnaire with two dimensions "Feeling hurt" and "Emotional distress", for future research only these items are important to evaluate disease specific QoL, omitting the other 26 items is acceptable. Lack of clinical effect of encasings on AA and AD resulted in a lack in improvement of QoL between the placebo and active treatment groups as measured with disease specific and generic questionnaires in both study populations (Chapter 4, 6, 7). Interestingly, within the AD population the disease specific QCSD and the generic SF-36 questionnaire revealed body-site specific effects of trunk and arms on QoL (Chapter 6, 7).

It is important to know that treatment of chronic diseases can improve QoL without improving clinical symptoms, for example due to better coping. Because of the chronic nature of AR, AA and AD, long lasting clinical improvement might be difficult to reach and it might be better to focus treatment on patient related QoL aspects. Improvement of QoL, due to patient guidance, can be related to disease specific QoL and /or general "well being", as measured with disease specific and generic questionnaires respectively. Combined with the conclusion that the disease specific QCSD and the generic SF-36 questionnaire measure different aspects of QoL (Chapter 5), it is recommendable to use both for evaluating treatment of individual patients in the future.

The background of measuring differences in QoL in evaluating a particular treatment is often to calculate the cost effectiveness of that treatment. Quality of Adjusted Life Year (QALY) is a composite indicator of additional life years gained from an intervention with a patients

judgement concerning the QoL in those years.[66;76] Improvement of QoL without a difference in gained additional life years between treatment groups could lead to a cost effectiveness of a particular treatment without improving clinical symptoms.

Main conclusions

The decrease in Der p1 + f1 in the Heideheuvel and DUMAS studies and combined lack of clinical improvement of AA and AD shows that there is no experimental basis for prescribing mattress encasings to AA and AD patients.

Questionnaires with atopic disease related items resulted in a good prediction of clinical atopic disease activity within a HDM sensitised population.

Active AD at arms and trunk decreases QoL, as practitioner it is important to keep this in mind when treating the AD patient.

The disease specific and the generic questionnaire should both be used to measure QoL in atopic dermatitis patients, not only do they measure different aspects of QoL but also because treatment of chronic atopic patients could improve different aspects of QoL without improving clinical symptoms.

Recommendations for future research

1 In adult atopic patients new treatment strategies should aim for inhibiting both Th1 and Th2 profiles and the effect on Th1 and Th2 cells should be monitored.
2 The study shows that using questionnaires with atopic disease related items on atopic patients have a reliability of about 80 % that specific atopic diseases are present. In the future, these items can be used for epidemiological and genetical studies.
3 The condensed 16-items QCSD QoL questionnaire should be further evaluated for use in clinical practice.

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Nederlandse samenvatting

Patiënten met allergische aandoeningen zoals allergische rhinitis (AR), allergisch astma (AA) en atopische dermatitis (AD) reageren op stoffen in hun omgeving die onschadelijk zijn voor het lichaam. Voorbeelden hiervan zijn huisstofmijt en graspollen, deze stoffen worden allergenen genoemd. Blootstelling aan deze stoffen kan leiden tot niezen en snotterigheid bij AR, tot benauwdheid bij AA en tot verergering van het eczeem bij AD. Het is aannemelijk dat vermijden van contact met allergeen zou kunnen leiden tot verbetering.
Doel van deze studie was om het effect van anti-allergische hoezen op de hoeveelheid huisstofmijt (HSM) allergeen, klinische variabelen en kwaliteit van leven (KvL) variabelen in een atopische populatie te onderzoeken.

In dit proefschrift worden twee studie populaties beschreven:

1. Patiënten met AA afkomstig van het astmacentrum Heideheuvel, dit was een mono-center studie
2. Patiënten met AA, AR en/of AD geselecteerd uit de drie studie centra Utrecht, Groningen, Rotterdam, die deelnamen aan een dubbelblinde placebo gecontroleerde multi-center studie naar HSM vermijdingsmaatregelen bestaande uit het toepassen van anti-allergische hoezen (Dutch Mite Avoidance Study, DUMAS).

In **Hoofdstuk 1** worden de kenmerken beschreven van de verschillende allergische aandoeningen. Daarnaast wordt een samenvatting gegeven van de wetenschappelijke studies die het effect van eliminatie van HSM allergeen beschrijven. Sommige studies zagen een verbetering van de allergische klachten en andere studies niet. Ook wordt de rol van kwaliteit van leven (KvL) vragenlijsten uitgelegd. Er wordt een onderscheid gemaakt in twee typen vragenlijsten, ziekte specifieke vragenlijsten, die de rol van bijvoorbeeld AA of AD op de KvL beschrijven, en generieke vragenlijsten, die juist in gaan op de algemene KvL en iets zeggen over het algemene welbevinden.
Hoofdstuk 2 beschrijft het fenotype van patiënten met hun allergische aandoeningen die deelnamen aan de Dutch Mite Avoidance Study (DUMAS). In totaal begonnen 325 patiënten met AR, AA en AD aan het onderzoek. Van de 325 patiënten had het grootste deel AR en AR gecombineerd met AA. De meerderheid had meer dan één allergische aandoening.
In **Hoofdstuk 3** wordt het effect van matrashoezen op AD beschreven in de DUMAS studie. Ondanks dat de hoeveelheid blootstelling aan HSM allergeen in bed en in de slaapkamer significant werd verlaagd, trad er geen verbetering van AD op. Onveranderde blootstelling aan allergenen op andere plekken waar mensen veel tijd doorbrengen zoals school, werk en buitenlucht zou het gebrek aan effect kunnen verklaren.
Hoofdstuk 4 beschrijft het effect van hoezen op allergeen specifieke parameters bij AA patiënten. Dit onderzoek werd uitgevoerd met AA patiënten in het astmacentrum Heideheuvel. De hoeveelheid HSM allergenen in de actief behandelde groep t.o.v. de placebo groep daalde significant. De allergeendrempel voor HSM was significant lager in de placebo groep t.o.v. de actief behandelde groep met hoezen.

In **Hoofdstuk 5** wordt eveneens een groep AA patiënten beschreven waarbij naast de longfunctie ook de klachtenscores van neus en longen, ochtend en avond piekstroom van de longen en KvL werd gemeten. Deze studie werd eveneens uitgevoerd in het astmacentrum Heideheuvel. Ondanks dat er een significante daling optrad in de hoeveelheid HSM allergeen in het bed werden ook hier tussen de placebo en hoezen groep geen verschillen gevonden in de gemeten variabelen.
Hoofdstuk 6 vergelijkt twee KvL vragenlijsten in de AD groep in de DUMAS studie, namelijk een AD specifieke vragenlijst en een veel gebruikte algemene KvL vragenlijst, de SF-36. Twee schalen die met deze vragenlijst worden gemeten zijn: 'Fysiek en mentaal lijden' en 'Emotionele stress'. Het bleek dat een aantal vragen van de AD specifieke vragenlijst, de Questionnaire of Coping with Skin Diseases (QCSD), niet relevant waren en waardoor de deze vragenlijst kan worden verkort van 42 naar 16 vragen. Verder bleek ook dat beide vragenlijsten voor een deel dezelfde maar ook verschillende aspecten van KvL meten. Het gebruik van beide vragenlijsten voor de allergische patiënten groep wordt derhalve aangeraden.
In **Hoofdstuk 7 en 8** worden de effecten van tijd, behandeling, geslacht, leeftijd en de eczeemscore van hoofd, romp, armen en benen op KvL als uitkomstvariabele gemeten in de AD groep van de DUMAS studie. In **Hoofdstuk 7** blijkt dat het hebben van AD op de armen en romp een negatief effect heeft op de fysieke en mentale schaal van de SF-36. **Hoofdstuk 8** beschrijft dat de aanwezigheid van AD op de armen ook een negatief effect heeft op de schalen 'Fysiek en mentaal lijden' en 'Emotionele stress' van de QCSD. Terwijl het hebben van AD op de romp alleen een effect heeft op 'Fysiek en mentaal lijden'.
In **Hoofdstuk 9** worden de onderzoeksgegevens samengevat en bediscussieerd. In dit hoofdstuk wordt eveneens de rol van andere prikkels die allergische aandoeningen kunnen induceren en verergeren beschreven, tevens wordt de interactie tussen genetische aanleg, omgevingsfactoren op het ontstaan van allergische aandoeningen besproken.

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Curriculum Vitae

Albert-Jan (Bert) Oosting werd geboren op 14 april 1968 in Hoogezand-Sappemeer. Hij behaalde het Atheneum-B diploma in 1986 aan de Winkler Prins scholengemeenschap in Veendam.

Daarna begon hij in 1986 aan de studie biologie aan de Rijksuniversiteit Groningen. Alwaar in 1992 het doctoraal examen medische biologie werd behaald. Tijdens de biologie studie maakte hij voor het eerst kennis met het onderwerp allergie, door de dichtheidsverdeling van eosinofiele en neutrofiele granulocyten van allergische patiënten over een Percoll dichtheidsgradiënt te onderzoeken onder leiding van dr. H.F. Kauffman.

In 1989 werd eveneens begonnen met de studie Geneeskunde aan de Rijksuniversiteit Groningen, waarin in 1995 het artsexamen werd behaald. In de periode 1992/1993 werd de propedeuse filosofie voor de universitaire bovenbouw gevolgd en gehaald.

In het Academisch Medisch Centrum te Amsterdam werd in 1995/1996 zeven maanden onderzoek gedaan naar het kloneren van drie clusters van het ‘Low Density Lipoproteine receptor eiwit’, naast het werk als arts-assistent bij de afdeling stollingsziekten. Vanaf 1996 werd in het astmacentrum Heideheuvel te Hilversum gekeken naar het effect van het graspollen seizoen op allergische neusklachten bij graspollen allergische patiënten, middels neusprovocatie en body plethysmografie verrichte neusweerstandsmetingen. Bovendien werd een deel van het in dit proefschrift beschreven onderzoek naar het effect van matrashoezen op huisstofmijt allergische astma patiënten uitgevoerd o.l.v. dr. M.S. de Bruin-Weller en L.H.M. Rijssenbeek-Nouwens.

Eind 1997 werd aan het Universitair Medisch Centrum Utrecht begonnen met de in dit proefschrift beschreven Dutch Mite Avoidance Study o.l.v. professor dr. C.A.F.M. Bruijnzeel-Koomen en dr. M.S. de Bruin-Weller, waarbij middels longfunctie testen, neusprovocatie testen en eczeem scores gekeken werd naar het effect van Goratex-hoezen op allergische aandoeningen.

In 1999 werd de twee jaar durende part-time opleiding ‘Hoger management voor de Gezondheidszorg’ afgerond.

In februari 2000 werd gestart met de opleiding Dermatologie en Venereologie in het Universitair Medisch Centrum Utrecht met als opleider professor dr. C.A.F.M. Bruijnzeel-Koomen.